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88-175444

BASIC PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 : C07D 221/14, A61K 31/435

A1

(11) International Publication Number: WO 88/ 04292

(43) International Publication Date: 16 June 1988 (16.06.88)

(21) International Application Number: PCT/US87/02866

(22) International Filing Date: 4 November 1987 (04.11.87)

(31) Priority Application Number: 940.703

(32) Priority Date: 11 December 1986 (11.12.86)

(33) Priority Country: US

(60) Parent Application or Grant
(63) Related by Continuation
US 940,703 (CIP)
Filed on 11 December 1986 (11.12.86)

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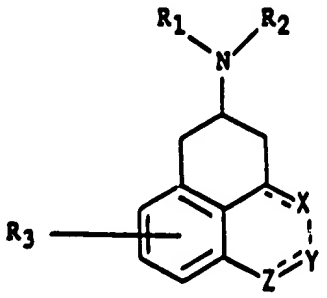
(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, SE (European patent), US.

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: ANTIPSYCHOTIC AMINO-POLYHYDRO-BENZ-(ISO)QUINOLINES AND INTERMEDIATES

NEW AMINO - POLY:HYDRO - BENZ-(ISO) QUINOLINE DERIVS + E.G. ETHYL TRANS-2,3,7,8,9a-HEXAHYDRO 1H BENZO (de)— QUINOLIN-1- CARBOXYLATE, USED AS ANTI PSYCHOTIC AGENTS

(AU) ISOQUINOLINE



(I)

B(6-D13, 12-C10).

(57) Abstract - 2759

Amino-polyhydro-benz-(iso)quinoline compounds of formula (I), wherein X, Y, Z, R_1, R_2, R_3 are as defined in the specification, e.g., 3aS-trans-5-(N,N-di-n-propylamino)-3a,4,5,6-tetrahydro-1H-benzo de quinolin-2(3H)one, or pharmacologically acceptable salts thereof, are useful as antipsychotic drugs or as intermediates for making such compounds. Pharmaceutical compositions and methods of using these compounds are also provided. Processes for preparing the compounds are provided.

88175444

ANTIPSYCHOTIC AMINO-POLYHYDRO-BENZ-(ISO)QUINOLINES AND INTERMEDIATES

INTRODUCTION

This invention relates to some partially hydrogenated, amino-substituted three ring organic chemical compounds, one of which rings contains a nitrogen therein in the 4-, 5- or 6- position of the ring structure, relative to the amino-group bearing ring carbon atom when it is numbered as being in the 2-position, as antipsychotic drug compounds, chemical intermediates therefor, to the use of such end product compounds as antipsychotic drugs and pharmaceutical compositions therefor. More particularly, this invention provides some new amino-group substituted polyhydro-benz-(iso)quinoline compounds which are useful as antipsychotic drug compounds, some chemical intermediate compounds to make such end product compounds, pharmaceutical compositions for such antipsychotic drug compounds and the new use of these end product compounds as antipsychotic drugs.

BACKGROUND OF THE INVENTION

Known commercially available, organic compounds (non-lithium containing drugs), e.g., prochlorperazine, thoridazine, thiothixene, fluphenazine, piperacetazine, trifluoroperazine are neuroleptic drugs. Neuroleptic drugs are known to exhibit, to a lesser or higher degree, extrapyramidal system side effects such as catalepsy, which side effects Central Nervous System (CNS) drug researchers would prefer to avoid.

Some 2-amino-2,3-dihydro-1H-phenalene derivative compounds, per se have been described in publications such as

(1) Chem. Scand., 19, 755 (1965), which shows an N-(methoxycarbonyl)amino-2,3-dihydro-1H-phenalene, but it does not disclose the compounds claimed herein or the antipsychotic use of this invention.

(2) Chim. Therap., 4, 95, (1969), discloses:

2-amino-1-oxo-2,3-dihydro-1H-phenalene hydrochoride,

2-(N-acetylamino)-1-hydroxy-2,3-dihydro-1H-phenalene,

2-amino-1-hydroxy-2,3-dihydro-1H-phenalene hydrochoride, and

2-(N-ethylamino)-1-hydroxy-2,3-dihydro-1H-phenalene,

but such publication does not disclose the compounds claimed herein or the antipsychotic drug use for the compounds disclosed herein.

(3) The Chimie Therapeutique, 6, 196, Mai-Juin, 1971, No. 3, discloses 2-amino-2,3-dihydro-1H-phenalene, 2-(N,N-dimethylamino)-2,3-dihydro-1H-phenalene, 2-(N-methylamino)-2,3-dihydro-1H-phenalene, but such publication does not disclose the antipsychotic use which has been found for the compounds disclosed therein.

(4) Evans,C. et al, Journal of the Chemical Society, Section C, Organic, (1971) pages 1607-1609, discloses N-ethyl-2,3-dihydro-4-methylphenalen-2-amine and how it is made but does not disclose any specific use activity for the compound.

(5) Derwent Abstract 85-165888/28 of W. German Patent Offen. 3,346,573-A discloses some 4-amino-tetrahydro-benzindoles as CNS medicaments, but it does not mention the compounds disclosed here or use as antipsychotic drugs.

More recently, co-assigned US patent application Serial No. 06/815,367, filed December 31, 1985 discloses and claims the use of some 2-amino-2,3-dihydro-1H- phenalene compounds as antipsychotic drug compounds, e.g., 2,3-dihydro-2-(N,N-di-n-propylamino)-1H-phenalen-5-ol, and salts of such compounds.

However, in contrast to the immediately above described phenalene-ring system compounds, the compounds claimed here have a heterocyclic ring system which are prepared by different chemical processes than are those previously described compounds. Also, the lead compounds of the above amino-phenalene ring system series have been found to have a higher than desired (more positive) result in a standard toxicology test, the Ames test. It is hoped that the compounds of this invention will show not only good ranges of antipsychotic activities in the standard tests therefor but will also show little or no positive result in the Ames test, which indicates reduced chances of toxicity of the drug compounds of this invention. To date, with the lead compound of interest now, that less positive Ames test result, compared to the leading 2-amino-phenalene compound, has been found to be true, while the compound also has antipsychotic activity in the same general range as the 2-(N,N-di-n-propylamino)-2,3-dihydro-1H-phenalen-5-ol compound referred to hereinabove.

The findings of this invention are believed to be unexpected and not generally predictable from prior known studies because some of

the amino-substituted polyhydro-benz-(iso)quinoline-type compounds close to the compounds claimed here have been found not to have sufficient antipsychotic activity to be considered further as possible antipsychotic drug compound candidates.

OBJECTS OF THE INVENTION

It is an object of this invention to provide some new amino-substituted-polyhydro-benz-(iso)quinoline compounds per se which have been found to be useful as antipsychotic drugs.

It is another object of this invention to provide a process or a method for treating human and valuable warm-blooded animal patients suffering from psychotic symptoms with an amount of one of the here-indefined amino-substituted-polyhydro-1H-benz-(iso)quinoline compounds or a pharmacologically acceptable salt thereof sufficent or effective to relieve the psychotic symptoms in said patient.

It is another object of this invention to provide pharmaceutical compositions containing at least one of the amino-substituted-polyhydro-benz-(iso)quinoline compounds therein as an active antipsychotic drug acting ingredient therein.

It is also an object of this invention to provide some new compounds per se which are useful in chemical processes to make the end product amino-substituted-polyhydro-1H-benz-(iso)quinolines of this invention.

SUMMARY OF THE INVENTION

Briefly, this invention provides some new compounds per se, of formula I herebelow, which are useful in appropriate pharmaceutical dosage unit forms, as drugs for treating patients suffering from psychotic symptoms to relieve those symptoms of psychoses in said patients, or as chemical intermediates for making such antipsychotic drug compounds.

This invention also provides a method or process for treating psychotic symptoms in human or valuable warm-blooded animal patients which comprises administering to such patient an amino-sustituted-polyhydro-benz-(iso)quinoline, of formula I herein below, or a pharmaceutically acceptable salt thereof, in an amount sufficient to relieve the symptoms of psychotic behavior in said patient.

This invention also includes compositions containing one of the

antipsychotically active compounds of formula I herebelow, or an acid addition salt thereof, in combination with appropriate diluents, which compositions are useful in appropriate dosage unit form to treat human or valuable warm-blooded animal patient suffering from psychotic symptoms to relieve those antipsychotic symptoms in said patient.

DETAILED DESCRIPTION OF THE INVENTION

More specifically, this invention provides new compounds of formula I (See chemical formula pages) where one of X, Y and Z is -$N(R_4)$- and the remainder of X, Y and Z is -$CH(R_5)$- or -C(O)-, and

when Z is -$N(R_4)$-, Y can be -$CH(R_5)$- or -C(O)-, and X will be -$CH(R_5)$-;

when Y is -$N(R_4)$-, X and Z will each be -$CH(R_5)$-;

when X is -$N(R_4)$-, Y and Z will each be -$CH(R_5)$-;

R_1 and R_2 are each hydrogen or C_1 to C_3-alkyl; or R_1 is hydrogen while R_2 is C_1 to C_4-alkyl, or

R_1 and R_2 are taken together with the nitrogen to which they are bonded to complete an N-azetinyl ring, an N-pyrrolidinyl ring, an N-piperidinyl ring or an N-morpholinyl ring;

R_3 is hydrogen or a substituent selected from the group consisting of a halogen having an atomic number of from 9 to 35;

C_1 to C_3-alkyl, C_1 to C_3-alkyloxy, trifluoromethyl, C_1 to C_3-alkylcarbonyloxy, phenylcarbonyloxy or benzylcarbonyloxy;

R_4 is part of a double bond when the ----- bond is double, or R_4 is hydrogen, C_1 to C_3-alkyl or -$C(O)OR_6$ when the ----- bond is a single bond;

R_5 is part of a double bond when the ----- is double, or R_5 is hydrogen when the ----- bond is a single bond;

R_6 is C_1 to C_3-alkyl or benzyl;

or an acid addition salt thereof.

In the above formula I compounds, the term "C_1 to C_2-alkyl" means the methyl and ethyl groups. The term "C_1 to C_3-alkyl" further includes n-propyl and isopropyl groups. The term "C_1 to C_4-alkyl" further includes the butyl group in its various isomeric forms. The term "C_1 to C_2-alkyloxy" means methyloxy and ethyloxy. The term "C_1 to C_2-alkyloxycarbonyl" means methoxycarbonyl ($CH_3OC(O)$-) or ethyl-

oxycarbonyl C_2H_5-OC(O)-. The term "C_1 to C_5-alkanoyloxy" means acetyloxy, propionyloxy, butanoyloxy or pentaoyloxy, e.g., CH_3COO- is acetyloxy.

Examples of acid addition salts of these compounds include the hydrohalide salts such as the hydrochloride, hydrobromide, hydrofluoride and hydroiodide, the sulfate and bisulfate, various phosphorus acid salts, the methanesulfonate, the p-toluenesulfonate, the benzoate, the acetate, and other alkanoic acid salts, as well as the salts of various dicarboxylic and tricarboxylic acids such as maleic, succinic, fumaric, malic, oxalic, itaconic acids, and the like. Some of these acids, e.g., oxalic acid, may be preferred for extracting the active amino or intermediate compound from its reaction mixture, while other acids, e.g., succinic, maleic or p-toluenesulfonic may be preferred when the resulting end product amine is to be formulated into pharmaceutically useful form. Also, the formula I compound and its acid addition salt in their crystalline state may sometimes be isolated as solvates, i.e., with a discrete quantity of water or other solvent such as ethyl acetate, ethanol, and the like, associated physically and thus removable without effective alteration of the active chemical drug entity per se.

If desired the formula I compounds of this invention can be resolved into their respective d- and l-optical isomers by methods known in the art. In this case, the optical resolution can be done by at least two different routes. The resolving agents by either route are any of the known resolving agents such as optically active dibenzoyltartaric acid, camphorsulfonic acid, bis-o-toluoyltartaric acid, tartaric acid, and diacetyl tartaric acid which are commercially available and which are commonly used for resolution of amines (bases), as for example in Organic Synthesis, Coll. Vol. V., p. 932 (1973), resolution of R-(+) and S-(-)-α-phenylethylamine with (-)-tartaric acid.

By one method for resolving the compounds of this invention, for example, one of the formula I, or other amine compounds can be converted into its optically active diastereomeric salts by reaction with an optically active acid - examples mentioned above - in a manner standard in the isomer resolution art. These diastereomeric

salts can then be separated by conventional means such as differential crystallization. Diastereomeric salts have different crystallization properties, which are taken advantage of in this separation. On neutralization of each diastereomeric salt with aqueous base the corresponding optically active enantiomers of the formula I amine or other amine compound can be obtained, each of which can subsequently and separately be converted as hereinafter described in the examples to the desired acid addition salt, if desired.

Alternatively an amine-containing precursor to a formula I compound can first be resolved as above and then converted to an optically active form of a formula I compound.

The compounds of interest for use as end product antipsychotic drug compounds are those of formula I where one of X, Y and Z is $-N(R_4)-$ and the remainder of X, Y and Z is $-CH(R_5)-$ or $-C(O)-$, and

when Z is $-N(R_4)-$, Y can be $-CH(R_5)-$ or $-C(O)-$, and X will be $-CH(R_5)-$;

when Y is $-N(R_4)-$, X and Z will each be $-CH(R_5)-$,

when X is $-N(R_4)-$, Y and Z will each be $-CH(R_5)-$;

R_1 and R_2 are each hydrogen or C_1 to C_3-alkyl, or R_1 is hydrogen while R_2 is C_1 to C_4-alkyl, or R_1 and R_2 can be taken together with the nitrogen to which they are bonded to complete an N-azetidinyl ring, or N-pyrrolidinyl ring, and N-piperidinyl ring or an N-morpholinyl ring;

R_3 is hydrogen or a substituent selected from the group consisting of

a halogen having an atomic number of from 9 to 35,

C_1 to C_3-alkyl,

C_1 to C_3-alkyloxy,

trifluoromethyl,

C_1 to C_3-alkyl-carbonyloxy,

phenylcarbonyloxy or

benzylcarbonyloxy;

R_4 is part of a double bond when the ----- bond is double, or R_4 is hydrogen, C_1 to C_3-alkyl, or $-C(O)OR_6$ when the ----- bond is a single bond;

R_5 is part of a double bond when the ----- bond is double, or R_5

is hydrogen when the ----- bond is a single bond;

R_6 is C_1 to C_3-alkyl or benzyl; such tha-

(1) when Z is -N(R_4)-, Y is -C(O)- and X is -CH(R_5), and R_1 and R_2 are each C_1 to C_3-alkyl, R_4 is hydrogen;

(2) when Y is -N(R_4)-, and X and Z are each -CH(R_5)-, and R_4 is part of a double bond, R_1 and R_2 are C_2 to C_3-alkyl, or R_1 is hydrogen while R_2 is C_2 to C_4-alkyl, or R_1 and R_2 are taken together with the nitrogen to which they are bonded to complete an N-azetidinyl ring, and N-pyrrolidinyl ring, and N-piperidinyl ring or an N-morpholinyl ring; and

(3) when Y is -N(R_4)- and X and Z are each -CH(R_5)-, and R_1 and R_2 are each C_1 to C_3-alkyl, R_4 is part of a double bond;

or a pharmaceutically acceptable salt thereof.

Preferred group of compound of this invention are those of formula I, where:

(a) X is -N($COOR_6$)-, Y is -CH_2-, Z is -CH_2- and R_6 is as defined hereinabove,

R_1 and R_2 are each hydrogen or lower alkyl; and

R_3 is hydrogen, C_1 to C_3-alkyloxy, fluorine, chlorine, bromine, hydroxy, C_1 to C_3-alkyl, C_1 to C_3-alkyloxycarbonyl, phenyloxycarbonyl or benzyloxycarbonyl, or pharmaceutically acceptable salts of such compounds;

(b) X is -CH_2-, Y is =N-, Z is -CH_2- and R_1, R_2 and R_3 are as defined immediately above in sub-section (a), or a pharmaceutically acceptable salt thereof, and

(c) X is -CH_2-, Y is -C(O), Z is -NH- and R_1, R_2 and R_3 are as defined in part (a) hereinabove, or a pharmaceutically acceptable salt thereof.

Examples of a specific compound within the preferred sub-groups (a), (b) and (c) are as follows:

(a) ethyl 8-(diethylamino)-2,3,7,8,9,9a-hexahydro-1H-benzo[de]-quinoline-1-carboxylate ester,

benzyl 8-(N-azetidinyl)-2,3,7,8,9,9a-hexahydro-1H-benzo-[de]quinoline-1-carboxylate ester,

methyl 8-(N-pyrrolidinyl)-2,3,7,8,9,9a-hexahydro-1H-benzo-[de]quinoline-1-carboxylate ester,

ethyl 8-(N-morpholinyl)-2,3,7,8,9a-hexahydro-1H-benzo[de]-quinoline-1-carboxylate;

(b) 5,6-dihydro-N,N-dimethyl-4H-benzo[de]isoquinolin-5-amine,

5,6-dihydro-4H-benzo[de]isoquinolin-5-(1-azetidine),

5,6-dihydro-4H-benzo[de]isoquinolin-5-(1-morpholine),

(c) 3aS-trans-5-(N,N-diethylamino)-3a,4,5,6-tetrahydro-1H-benzo[de]quinolin-2(3H)one,

3aS-trans-5-(N-azetidinyl)-3a,4,5,6-tetrahydro-1H-benzo-[de]quinolin-2-(3H)one,

3aS-trans-5-(1-pyrrolidinyl)-3a,4,5,6-tetrahydro-1H-benzo-[de]quinolin-2(3H)one,

3aS-trans-5-(N,N-dimethylamino)-3a,4,5,6-tetrahydro-1H-benzo[de]quinolin-2(3H)one,

and addition salts thereof, particularly pharmaceutically acceptable salts thereof.

The lead and most important end product compound to date of interest as a possible antipsychotic drug candidate is a compound of formula I wherein X is $-CH_2-$, Y is -C(O)-, Z is -NH-, so that the ----- bonds in that ring are each single bonds, R_1 and R_2 area each n-propyl, and R_3 is hydrogen, or a pharmaceutically acceptable salt thereof.

The compounds of formula I can be prepared by a variety of processes starting from an R_3-ring-unsubstituted or R_3-ring substituted 3-carboxy-1(2H,4H)naphthalenone, or an ester thereof, such as a 3-(C_1 to C_6-alkyloxycarbonyl)-1(2H,4H)naphthalenone, e.g., the methyl ester, or an equivalent benzyl ester thereof, or the like. Such starting materials can be prepared from aliphatic di-ester starting materials by known procedures or by procedures outlined in attached Chart A, hereinbelow.

The B. A. Hathaway et al article "A...Analogue of Amphetamine: 2-Amino-1,2-dihydronaphthalene" in J. Med. Chem. (1982), 25, No. 5, pp. 535-538 discloses how to make 1,2,3,4-tetrahydro-4-oxo-2-naphthalenecarboxylic acid for use as a chemical intermediate. Also, R. D. Haworth et al in an article entitled "Synthesis of 4-Hydroxy-2-naphthoic Acids" in J. Chem. Soc. (London) 10, (1943), pp. 10-13, discloses how to make 4-hydroxy-2-naphthoic acid, a starting mater-

ial, from benzylsuccinic acid.

Referring to Chart A for general reference, and to detailed Example 2 for exemplification an ethyl succinate ester such as a C_1 to C_6-alkyl or benzyl ester, e.g., the diethyl acetylsuccinate ester, can be alkylated with ring R_3-substituted or R_3-unsubstituted benzyl halide, e.g., benzyl bromide, to form the 1-acetyl-1-(R_3-phenylmethyl)butenedioate ester, shown at the end of step A in Chart A. In step B, the ester is subjected to a hydrolysis to remove the ester groups and to a cleavage reaction to remove the acyl group, e.g., with acid such as hydrochloric acid to form the di-acid shown at the end of step B. In step C the di-acid is cyclized by treatment with a strong acid, e.g., sulfuric acid, to form the bicyclic keto acid shown at the end of step C, e.g., 1,2,3,4-tetrahydro-4-oxo-2-naphthenoic acid. Thereafter in optional step D, the acid is esterified by known procedures with an appropriate alcohol in the presence of an esterification catalyst or by the use of selected alkyl or benzyl halide, e.g., methyl iodide or benzyl bromide, to obtain the desired ester, e.g., methyl 1,2,3,4-tetrahydro-4-oxo-2-naphthenoate ester, which can then be used as a starting material to make the compounds of interest for this invention.

The 5-Amino-tetrahydrobenzo[de]quinolin-2(3H)one compounds of this invention, that is, compounds where the aza-ring nitrogen is in the 6-position, relative to the ring carbon atom bearing the amino-nitrogen group when such is numbered as being the 2-position of such ring system, can be prepared by procedures outlined in Chart B hereinbelow, and exemplified in detailed Example 1.

Following the chemical structures in Chart B, the keto-ester from Chart A can be subjected first to a Reformatsky addition (See The Merck Index, 10th Ed., (1983) pp. ONR 74-75), followed by a hydrogenolysis and then a hydrolysis reaction to form the hydrogenated naphthyl-di-carboxylic acid compound shown at the end of step A. Then in step B that dicarboxylic acid compound is subjected first to an acid halide formation and then to a Friedel-Crafts acylation to form the keto-acenaphthylcarboxylic acid shown at the end of step B. The resulting keto-acenaphthyl-carboxylic acid can then be subjected in step C to a Schmidt ring expansion (lactam formation) reaction

(See The Merck Index, 10th Ed., (1983) pp. ONR 81-82) to form the tricyclic ring lactam-containing compound shown at the end of step C. Then the shown tricyclic lactam can be subjected in step D to a Curtis Rearrangement reaction (See The Merck Index, 10th Ed., (1983) p. ONR-21) to form the urethane/or carbamate ester) with the selected alcohol, e.g., tert-butanol. Then, in step E, the urethane group is cleaved with an acid, e.g., with trifluoroacetic acid, to form the amine group on the compound shown at the end of step E.

Then, in step F, optionally the tricyclic-lactam-amine shown at the end of step E can alternately be subjected either to reductive alkylation with formaldehyde or a variant thereof, to form the N,N-dimethylamino-derivative compound (step F_1) or to amino-nitrogen alkylation procedures (F_2) to form the N-higher monoalkyl (>than methyl), or N,N-di-C_1 to C_4-n-alkylamino with the selected alkyl halide, e.g., ethyl bromide, n-propyl bromide, isopropyl bromide, n-butylbromide, or an N-(mono-branched C_3 to C_4 alkyl, e.g., isobutyl bromide tert-butyl bromide, or with a 1,3-dibromopropane, 1,4-dibromobutane, 1,5-dibromopentane, or with 1,5-dibromo-3-oxopentane to form the desired cyclic amine compounds such as the N-azetidinyl, N-pyrrolidinyl, N-piperidinyl or N-morpholinyl amine compound where each of R_9 and R_{10} is one of the defined R_1 and R_2 groups other than hydrogen. As shown in the detailed examples our preferred amino group compounds for end product antipsychotic activity drug compounds are the N,N-di-n-propyl-amino- compounds.

To prepare the compounds having the aza-ring nitrogen in the 5-position relative to the ring carbon bearing the amino nitrogen in the 2-position, reference is made to Chart C, and detailed Example 2 for exemplification.

Starting in Chart C with the partially hydrogenated keto-ester (from Chart A, referred to hereinabove), the keto-ester is subjected first to a cyanohydrin formation reaction and second to a hydrogenolysis to convert the keto group to a cyano group and to form the compound shown at the end of step A. In step B, the cyano-ester is amidated to convert the ester group to an amide group, for which both of the cis- and trans-isomers are shown at the end of step B. The cis- and trans-isomers can be separated by known procedures, or used

as the mixed or racemic mixture in the next step C. In step C the cyano-amide compound(s) are subjected to a Hofmann Reaction (See The Merck Index, 10th Ed. (1983), page ONR 45) to form the respective cis-, trans- or mixed isomer cyano-amine compounds shown at the end of step C. As shown in connection with the amine formation steps in Chart B, the cyano-amine products can be subjected to a) reductive amination with formaldehyde to form the cyano-N-methylamino- or N,N-dimethylamino-compounds or b) to N-alkylation procedures described hereinabove to form the $-NR_9R_{10}$ amine compounds referred to herein, where R_9 and R_{10} are each C_1 to C_3-alkyl or R_9 is hydrogen while R_{10} is C_1 to C_4-alkyl or R_9 and R_{10} are taken together with the nitrogen to which they are bonded to complete an N-azetidinyl, an N-pyrrolidinyl, an N-piperidinyl or an N-morphilinyl ring; shown at the end of step D in Chart C. The cyano-amine compound from step D can then be subjected in steps E, F, G and H to a series of steps to form the three ring compounds of this invention. In step E, the cyano (nitrile) group is reduced to form an aminomethyl group, shown at the end of step E, which aminomethyl compound is then treated with formic acetic mixed anhydride or ethyl formate to form the formylamidomethyl amine compound shown at the end of step F. In step G the formyl-amido-amine compound cyclized with a strong acid, e.g., with polyphosphoric acid, to form the partially unsaturated 5-position-nitrogen-ring, three ring compound shown at the end of step G. In step H, the tricyclic amine compound from step G is subjected to catalytic dehydrogenation to dehydrogenate the aza-nitrogen ring further to form the compound shown at the end of step H, an end product compound of this invention. If desired the end product amine can be purified by chromatography or treated with an acid to form an acid addition salt to assist removing it from its reaction mixture, and then the amine can be re-sprung from the acid addition salt to the free amine, and then the amine can be re-converted to a selected acid addition salt form which will be pharmacologically and pharmaceutically acceptable for making formulations acceptable for dosage form preparation.

Chart D outlines and Example 4 exemplifies have to make compounds where the aza-ring nitrogen is in the 4-position relative to

the position of the ring structure carbon atom which bears the amino group if such ring carbon atom is numbered as being in the 2-position.

According to this process (Chart D) the partially hydrogenated naphthalene keto acid starting material (from Chart A) is amidated, e.g., by treatment first with an alkyl haloformate such as isobutyl chloroformate, and then with ammonium hydroxide to form the keto-amide, product of step A, e.g., the 3-carbamoyl-α-tetralone amide. The resulting keto-amide is then treated to effect imine formation in place of the keto group, e.g., by reaction with a dialkyloxyalkylamine in the presence of a tertiary amine, such as by reaction with a dimethoxyethylamine in the presence of triethylamine to form the 3-carbamoyl-1-[2-(dialkyloxyethyl)imino]tetralone as the product of step B. The resulting carbamoylimine compound is then treated in step C to reduce the imino nitrogen to its amino state, e.g., by reaction with an alkali metal borohydride, to form the corresponding 4-(dialkyloxyethylamino)-1,2,3,4-tetrahydro-2-naphthalenecarboxyamide as product of step C. This amino-carboxamide can be isolated into its cis- and trans-stereo isomers if desired, but the mixed stereo isomers can also be used as such in the next step. In step D, the dialkyloxyethylamino-tetrahydro-2-naphthalene carboxamide is treated in step D first with a strong acid such as sulfuric acid to effect cyclization to form the third ring and then with hydrogen in the presence of a reducing catalyst such as palladium on carbon to form the saturated third ring amide compound, shown as the product of step D, such as 2,3,7,8,9,9a-hexahydro-1H-benz[de]quinoline-8-carboxamide, which can be converted to a salt thereof, e.g., the hydrochloride salt, if desired. In step E, the three ring amide compound from step D is treated to effect urethane group formation on the aza-ring nitrogen atom, e.g., by treatment with an alkyl haloformate, e.g., ethyl chloroformate, in the presence of a tertiary amine such as triethylamine to form the urethane as a product of step E, such as trans-ethyl 8-(aminocarbonyl)-2,3,7,8,9,9a-hexahydro-1H-benzo[de]-quinoline-1-carboxylate ester. Then, in step F, this urethane ester is subjected to a Hofmann Reaction, as described hereinabove, e.g., by treatment with bis(trifluoroacetoxy)iodobenzene to convert the

amide group to an amine group and to form the amino-urethane ester such as 8-amino-2,3,7,8,9,9a-hexahydro-1H-benzo[de]quinoline-1-carboxylate ester. In step G, that amino-urethane ester can be treated to effect reductive alkylation with formaldehyde to form the N,N-dimethylamino tertiary amine (shown in Chart D) or subjected to reaction with alkyl iodide or alkyl bromide, or with a 1, 3 to 5-dihalo-C_3 to C_5-alkane or a 1,5-dihalo-3-oxo-pentane to form the respective higher alkyl or cyclic tertiary amine groups as described hereinabove (not shown in Chart D). Thereafter, in step H, the tertiary-urethane can be treated to reduce the urethane group to a methyl group, e.g., with an alkali metal aluminum hydride, such as lithium aluminum hydride to form the 2,3,7,8,9,9a-hexahydro-N,N,1-trimethyl-1H-benzo[de]quinolin-8-amine, which can be converted to an acid salt, e.g., with hydrochloric acid, to assist separation of this cyclic diamine from its reaction mixture.

A procedure for preparing a tricyclic, aza-ring containing primary amine compound having the aza-ring nitrogen in the 4-position relative to the ring carbon atom bearing the amino group is set forth generally in Chart E and is exemplified by detailed Example 5.

Starting with a 4-(dialkyloxyethylamino)-1,2,3,4-tetrahydro-2-naphthalenecarboxamide (from Chart D), cyclization can be effected in step A with a strong acid such as sulfuric acid followed by catalyzed dehydrogenation, such as by bubbling air through the reaction mixture in the presence of a palladium on carbon catalyst, to form 8,9-dihydro-7H-benzo[de]quinoline-8-carboxamide. Then in step B the resulting tricyclic carboxamide can be subjected to alkaline hydrolysis to convert the carboxamide to the corresponding tricyclic carboxylic acid, such as 8,9-dihydro-7H-benzo[de]quinoline-8-carboxylic acid. In step C, the carboxylic acid is subjected to a Curtis Reaction (step C1) to convert the carboxylic acid group to an carbonylazide group which carbonyl-azide is converted (step C2) to the isocyanate group intermediate with heat, followed by conversion (step C3) of the cyanate group to the urethane group with a selected alcohol such as methanol to form the corresponding carbamate ester. In step D, the carbamate ester is subjected to alkaline hydrolysis to convert the carbamate ester to the primary amine.

The primary amine is useful as a chemical intermediate to form the N-mono-C_1 to C_4-alkylamines, or the N,N-di-C_1 to C_3-alkylamines by procedures known in the art or as described herein. Also, such primary amines can be used as a chemical intermediate to form the cyclic amine group compounds with 1,3-dihalopropane, 1,4-dihalobutane, 1,5-dihalopentane or 1,5-dihalo-3-oxo-pentane to form respectively the N-azetidinyl, the N-pyrrolidinyl, the N-piperidinyl and the N-morpholinyl derivative compounds.

This invention also relates to compositions containing a new secondary or tertiary amine (at least one of R_1 and R_2 being other than hydrogen) formula I compound as an active ingredient in a pharmaceutical carrier. The compositions are useful in pharmaceutical dosage unit forms of the selected formula I compounds for local (topical) and systemic administration (oral, rectal and parenteral administration form) in therapy for treating an alleviating symptoms of psychoses in humans and valuable animals, including dogs, cats and other commercially valuable and domestic animals.

The term "unit dosage form" as used in this specification and in the claims refers to physically discrete units suitable as unitary dosages for mammalian subjects, each unit containing a predetermined quantity of the essential active ingredient compound of this invention calculated to produce the desired effect, in combination with the required pharmaceutical means which adapt the said ingredient for systemic administration. The specification for the novel unit dosage forms of this invention are dictated by and directly dependent on the physical characteristics of the essential active ingredient and the particular effect to be achieved in view of the limitations inherent in the art of compounding such an essential active material for beneficial effects in humans and animals as disclosed in detail in this specification under exemplified embodiments, these being features of the present invention. Examples of suitable unit dosage forms in accordance with this invention are tablets, capsules, orally administered liquid preparations in suitable liquid vehicles, sterile preparations in suitable liquid vehicles for intramuscular and intravenous administration, suppositories, and sterile dry preparations for the extemporaneous preparation of sterile injectable preparations in

a suitable liquid vehicle. Suitable solid diluents or carriers for the solid oral pharmaceutical unit dosage forms are selected from the group consisting of lipids, carbohydrates, proteins and mineral solids, for example, starch, sucrose, lactors, kaolin, dicalcium phosphate, gelatin, acacia, corn syrup, corn starch, talc and the like. Capsules, both hard and soft, are filled with compositions of the selected formula I compound or salt thereof ingredients in combination with suitable diluents and excipients, for example, edible oils, talc, calcium carbonate and the like and also calcium stearate. Liquid preparations for oral administration are prepared in water or aqueous vehicles which advantageously contain suspending agents, for example, methylcellulose, acacia, polyvinylpyrrolidone, polyvinyl alcohol and the like. In the case of injectable forms, the injectable formulation must be sterile and must be fluid to the extent that easy syringeability exists. Such preparations must be stable under the conditions of manufacture and storage, and ordinarily contain in addition to the basic solvent or suspending liquid, preservatives in the nature of bacteriostatic and fungistatic agents, for example, parabens, chlorobutanol, benzyl alcohol, phenol, thimerosal, and the like. In many cases, it is preferable to include osmotically active agents, for example, sugars or sodium chloride in isotonic concentrations. Carriers and vehicles include vegetable oils, ethanol, polyols, for example, glycerol, propylene glycol, liquid polyethylene glycol, and the like. Any solid preparations for subsequent extemporaneous preparation of sterile injectable preparations are sterilized, preferably by exposure to a sterilizing gas, for example, ethylene oxide. The aforesaid carriers, vehicles, diluents, excipients, preservatives, isotonic agents and the like constitute the pharmaceutical means which adapt the preparations for systemic administration.

For psychotic, including schizophrenic, disease, a daily dose of 1 to 700 mg of a formula I compound is indicated, preferentially 10 to 200 mg; in units of two or three or four subdivided doses, and the exact amount is adjusted based on the weight, age and condition of the patient.

The pharmaceutical unit dosage forms are prepared in accordance

with the preceding general description to provide from about 0.5 mg to about 100 mg of the essential active ingredient per unit dosage form. The amount of the essential active ingredient provided in the pharmaceutical unit dosage forms is based on the finding that the effective amount of 3aS-trans-5-(N,N-di-n-propylamino)-3a,4,5,6-tetrahydro-1H-benzo[de]quinolin-2(3H)-one, (U-72717) pharmacologically acceptable salt thereof, such as the 4-methylbenzenesulfonate salt, (U-72717E) a representative example of the compounds of the invention for obtaining an antipsychotic effect in humans is expected to be within the range from about 0.01 mg/kg to about 10 mm/kg, preferably 0.06 to 1.0 mg/kg.

The active ingredients of this invention can also be compounded in combination with other ingredients. The amount of such other active ingredients is to be determined with reference to the usual dosage of each such ingredient. Thus, these active compounds can be combined with hypotensive agents such as α-methyldopa (100-250 mg); with diuretics such as hydrochlorothiazide (10-50 mg); tranquilizers such as meprobamate (200-400 mg), diazepam (2-10 mg), muscle relaxants, such as carisoprodol (200-400 mg).

The compounds listed below were tested and found to have possible useful anti-psychotic activity properties as indicated by their having CNS test result, ED_{50} numbers of less than 50 mg/kg values in the known Hypothermia and/or the Apomorphine Antagonism test. The lower ED_{50} data numbers in these tests or in the amphetamine antagonism test is believed to be an indication of whether the compound acts by pre-synaptic agonist mechanism or by a dopamine receptor antagonist mechanism in accomplishing its antipsychotic drug effect. Most of these compounds also show some analgesic potency in standard analgesic laboratory animal tests.

The Effect on Body Temperature (Hypothermia) Test and the Antagonism of Apomorphone-Induced Case Climbing (ACC), (Apomorphine Antagonism Test) are described on page 1398 of the publication, Journal of Medicinal Chemistry, Vol. 22, No. 11, pp. 1390-1398, in an article entitled "6-Aryl-4H-s-triazolo[4,3-a][1,4]benzodiazepines... Action" by J. B. Hester, Jr., et al.

For the tests here, the Hypothermia Test procedure was run as

follows:

A group of four CF-1 male mice (18-22 g each) was injected intraperitoneally with the test compound prepared in 0.25 percent w/v methylcellulose in water solution. After 45 min, abdominal temperature of each mouse was measured using a thermister probe. A control group of four mice was treated with vehicle only and the temperature of the control group was taken in a similar manner. A compound was considered to have a significant effect on body temperature if the mean temperature in the test compound treated group deviated more than 3.5°C from the mean temperature of the parallel control group. Stimulants tend to elevate temperatures; depressants tend to lower body temperature.

As an example, when tested in this hypothermia test, the compound 3aS-trans-5-(N,N-di-n-propylamino)-3a,4,5,6-tetrahydro-1H-benzo[de]quinolin-2(3H)-one, as its 4-methylbenzenesulfonate salt (U-72717E), above, of this invention caused hypothermia in the test mice, with a calculated ED_{50} of 0.2 mg/kg of body weight. The test data appear to suggest that the hypothermic effect of U-72717E is the result of the activation of dopamine receptors, since the known dopamine blocker, haloperidol, also significantly blocks the hypothermia effect induced by U-72717E.

These results suggest usefulness of the amino-polyhydro-benzo-(iso)quinoline compounds, claimed herein, as anti-psychotic drug compounds within useful dosage ranges.

Another test which is used to predict antipsychotic activity of test compounds is termed a dopamine autoreceptor agonist activity test in which the test compound is screened in mice for presumed dopamine autoreceptor agonist activity based upon the ability of low (0.1 mg/kg or lower) doses of the test compound to antagonize the locomotor caused by d-amphetamine.

In this antagonism of d-amphetamine stimulation test, pairs of male Carsworth Farm (CF-1) mice (18 to 22 qm weight) are randomly assigned to Woodward circular actophotometer cages. After 30 minutes of acclimation, the mice are injected subcutaneously with 1 mg/kg of d-amphetamine and the indicated treatment (10 ml/kg) of test drug in Vehicle #122, (a 0.25 percent w/v carboxymethylcellulose in water

suspension) containing the desired test dosage of the drug compound, or placebo, and then the mice are returned to the cages. Starting 10 minutes after the injections, their locomotor activity is recorded for a period of 20 minutes. Nine treatment groups (n = 12, 24 mice/-group) including appropriate controls, are run for each experiment. The test results are expressed as percent change from d-amphetamine control groups. The statistical significance of these percent changes is determined by comparing the groups with Student's t-test with $p < 0.05$ considered indicative of a significant change.

The results of these tests with compounds of this invention, compared against known autoreceptor agonists (a) apomorphine, (b) 3-(-)-(1-propyl-3-piperidinyl) phenol, monohydrobromide [3(-)PPP] and (c) 3-(+)-(1-propyl-3-piperidinyl)phenol, monohydrobromide [3(+)PPP] are listed below:

In these tests, we consider that to be of possible practical interest as an antipsychotic drug compound, the compound should have a percentage change from the control of at least -25 percent at the 0.1 mg/kg dose test rate. Thereafter, other considerations such as possible toxicity, ease of preparation, pharmaceutical formulation properties and other factors may affect the choice of the lead drug candidate compound for more advanced clinical testing. As of now, we are considering U-72717E (Example 2) compound and possibly other pharmaceutically acceptable salts of that amine as our leading candidate, based upon potency in this test, and a low positive result in the Ames test.

The methods for preparing the compounds of this invention are further exemplified by the following detailed examples which are not intended as being limiting on the scope of the invention. All temperatures are in degrees Celcius unless otherwise indicated. Letter symbols are used in some places for brevity in references to common chemical reagents and analytical procedures. For example, IR means infrared, UV means ultraviolet, NMR means nuclear magnetic resonance and Exact Mass refer to type of spectral analyses. Similarly, THF means tetrahydrofuran, ether, used alone, means diethyl ether, petroleum ether means a commercial solvent having the indicated boiling range. The symbol MeOH means methanol, EtOAc means

ethyl acetate, and the like. In NMR analyses, the term ($CDCl_3$-TMS) means using deuterochloroform as solvent to lock on to hydrogens, and tetramethylsilane as the internal reference point in the NMR spectrum, Hz means NMR Hertz units. A reference to NMR (DMSO-d^6-TMS) refers to an NMR spectral analysis using dimethylsulfoxide solvent wherein the hydrogens of the methyl groups are deutero-hydrogens (6 of them) and again using tetramethylsilane as the internal standard. VPC means vapor phase chromatography analysis. The term "celite" has been used to indicate the use of a Celite™ brand of a filter aid.

Example 1 Preparation of 5,6-Dihydro-N,N-dipropyl-4H-Benz[de]-isoquinolin-5-amine, (E)-2-butenedioate (2:3) and 8,9-Dihydro-N,N-dipropyl-7H-Benz[de]isoquinolin-5-amine (E)-2-butenedioate (1:1).

A. Preparation of Diethyl 1-Acetyl-1-(phenylmethyl)butanedioate:

Sodium hydride (50% in mineral oil; 16.8 g, 0.35 mol) was washed twice with 200 mls of petroleum ether and covered with 800 mls of THF. The suspension was degassed with argon, and a degassed solution of diethyl acetylsuccinate (70.0 g, 0.324 mol) in THF (200 mls) was added to the water cooled suspension over a 10 minute period. The reaction mixture was stirred for 30 minutes at room temperature at which time the sodium hydride was depleted. Benzyl bromide (39.0 mls, 56.1 g, 0.328 mol) was added over a 1 minute period, and the solution was stirred at room temperature for 22 hours. The reaction mixture was diluted with hexane and washed twice with water and once with saturated NaCl solution, and the solution was dried ($MgSO_4$). The solvent was removed in vacuo to leave a yellow oil. The excess benzyl bromide was distilled from the compound (steam bath, 0.1 mm Hg) to leave the desired sub-titled diester compound (79 g). VPC analysis (1/8" X 3' column packed with 3% SE-30) (methylsilicone on 100/120 mesh gas-chrom Q as the stationary phase), flow rate 20 mls of nitrogen per minute, programmed: 100°C, 1 min; 100°C to 250 °C, 20°C per min; 250°C for 5 min) showed 3.09 min (1.4%), 4.59 min (20.4%), 5.45 min (78.2%). NMR ($CDCl_3$-TMS) δ1.24 (t,j=7.2 Hz,6,O-C-CH_3); 2.34 (s,3,$COCH_3$); 2.83 (s,2,$PhCH_2$); 3.06,3.24,3.34,3.51 (ab,2,-OOC-CH_2); 4.10,4.18 (d of t, 4, O-C-CH_2); 6.92-7.30 (m, 5, aromatic

H).

B. Preparation of (Phenylmethyl)butanedioic acid:

A mixture of the diester (79.0 g, 0.26 mol) from part A hereinabove, sodium hydroxide (280 g, 7.0 mol), and water (1900 mls) was refluxed for 48 hours and allowed to stand for 48 hours. The reaction mixture was washed with 1:1 THF/ether and acidified with concentrated HCl while cooling in ice. After stirring for 1 hour at 0°C, the precipitate was filtered, washed 3 times with water, and dried in vacuo at 80°C to give 63.5 g of a white solid. The compound contained sodium chloride. The compound was boiled in 800 mls of acetone and filtered. This was repeated on the precipitate, and the combined filtrate was evaporated to dryness in vacuo to leave the sub-titled di-carboxylic acid as an off-white solid (44.38 g, 66%). A sample (5 g) was crystallized from water to give off-white plates (4.78 g, mp. shrinks ~150°C, melts 159-161°C). NMR (Acetone-d^6, TMS) δ2.15-3.2 (m, aliphatic H), 7.26 (s, aromatic H). IR =CH 3022; Acid OH ~3000 broad, 2762, 2658, 2554; C=O 1720, 1700; C=C 1604, 1585, 1499; C-O 1226; Acid OH 917; γCH 756, 703. UV (Ethanol) 208 nm (E 8,200), 243 (94), 248 (125), 253 (167), 258 (204), 261 sl. sh. (162), 264 (162), 268 (115). Mass spec. m^+ at m/z 208.

Exact Mass Calcd. for $C_{11}H_{12}O_4$: 208.0736. Found: 208.0735.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.46; H, 5.81. Found: C, 63.60; H, 5.94.

C. Preparation of 1,2,3,4-Tetrahydro-4-oxo-2-naphthenoic acid:

A mixture of the diacid (34.33 g, 0.165 mol) from part B hereinabove and concentrated sulfuric acid (250 mls) was stirred at room temperature for 2 hours, and crushed ice (600 g) was added over 10 minutes. The crystallizing mixture was stirred at 4°C overnight and filtered. The crystals were washed well with water and dried in vacuo at 80°C to give an off-white solid (19.78 g, 63%). A sample (1.5 g) was crystallized from water to give the sub-titled 4-oxo-2-naphthenoic acid as an off-white solid (1.39 g, mp. 147-148.5°C). NMR (DMSO-d^6,TMS,D_2O) δ2.2-2.38 (m,2,Phenyl-CH_2), 3.1-3.3 (m,3,-CO-CH_2-CHCOO), 7.2-7.95 (m,5,aromatic H). IR =CH 3083,3054,3026; acid OH ~3000 broad, 2743, 2659, 2624, 2605, 2555, 2471, 2433; C=O 1694, 1688; C=C 1600; C-O/other 1317, 1286, 1260, 1226; acid OH/other

924; γCH/other 779,772. UV (Ethanol) 207 nm (E 25,250), 249 (11,700), 293 (1,700). Mass spec. m^+ at m/z 190.

Exact Mass Calcd. for $C_{11}H_{10}O_3$: 190.0630. Found: 190.0627.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found:C, 68.98; H, 5.29.

Anal. Calcd. for $C_{11}H_{10}O_3 \cdot 0.07\ H_2O$: C, 69.01; H, 5.34.

D. Preparation of Methyl 1,2,3,4-Tetrahydro-4-oxo-2-naphthenoic acid, methyl ester:

A mixture of the sub-titled 4-oxo-2-naphthenoic acid (18.28 g, 0.0961 mol) from part C hereinabove, potassium carbonate (15.94 g, 0.115 mol), methyl iodide (18.7 mls, 0.30 mol), and acetone (600 mls) was stirred at reflux for 3.5 hours on the steam bath. Methyl iodide (18.7 mls) was again added, and the mixture was refluxed overnight. The solvent was removed in vacuo, and the residue was partitioned between water and ether. The aqueous layer was again extracted with ether, and the combined organics were washed with sat. NaCl and dried ($MgSO_4$). The solvent was removed in vacuo to leave a yellow oil (19.4 g, 99%). A sample was purified via Kugelrohr distillation (0.05 mm Hg, 160-190°C) to give a light yellow oil (1.42 g). NMR ($CDCl_3$-TMS) δ2.73-3.3 (m, 5, CO-CH_2-CH-CH_2), 3.72 (s,3, OCH_3), 7.15-7.6 (m,3,aromatic H), 7.9-8.1 (m, 1, 5-aromatic H). IR =CH 3067, 3027, 3006; CH 2954, 2903, 2849; C=O (ester) 1735; C=O (ketone) 1687; C=C 1604, 1482; C=C/CH def. 1456, 1439; C-O/other 1288, 1270, 1251, γCH/other 766, 741. UV (Ethanol) 207 (23,550), 249 (11,850), 293 (1,700). Mass spec. m^+ at m/z 204.

Exact Mass Calcd. for $C_{12}H_{12}O_3$: 204.0786. Found: 204.0792.

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92. Found: C, 70.48; H, 6.09.

The reaction was repeated using the acid (50.0 g, 0.263 mol), methyl iodide (149 g, 1.05 mol), potassium carbonate (43.6 g, 0.316 mol) and acetone (1.25 l) at reflux for 17 hours. The crude material (61.5 g) was crystallized from ether/pet. ether at -78°C to give 44 g (71.4%) of the sub-titled ketone ester as crystals (mp 33-34°C).

E. Preparation of Lithium cyanide:

Lithium hydride (4.14 g, 50% in mineral oil, 0.26 mol) was washed twice with 100 mls of hexane and covered with 200 mls of THF.

A solution of acetone cyanohydrin (21.9 mls, 0.24 mol) in THF (100 mls) was added slowly while cooling in a water bath (~15°C). After the addition was complete, the water bath was removed and the reaction mixture was stirred at room temperature for two hours. The solvent was removed in vacuo at 95°C (steam bath) and dried in vacuo at room temperature overnight.

F. Preparation of Methyl 1,2,3,4-Tetrhydro-4-cyano-2-naphthalenecarboxylate:

The lithium cyanide prepared was suspended in THF (200 mls), and a mixture of the ketone ester, prepared as described in part D hereinabove (24.51 g, 0.120 mol) and diethyl phosphorylcyanide (35 g, 0.21 mol) in THF (450 mls) was added. The lithium cyanide dissolved to form a brown homogeneous solution. The mixture was stirred for 15 minutes, and hexane (500 mls) was added. The mixture was washed twice with water, and the aqueous washings were back extracted with ether. The combined organics were washed with saturated NaCl and dried ($MgSO_4$). The solvent was removed in vacuo to leave a yellow oil (46.83 g). The compound was dissolved in absolute ethanol (720 mls) containing 5 g of 10% palladium on carbon catalyst and hydrogenated in a Parr apparatus with a starting hydrogen pressure of 46 psi. After 3.25 hours, the reaction mixture was filtered through a filter aid (Celite™), and the catalyst was washed well with ethanol. The solvent was removed in vacuo to leave an oil which was dissolved in ether (300 mls) and washed 3 times with 4% NaOH. The aqueous washings were back extracted with ether, and the combined organics were washed with sat. NaCl and dried ($MgSO_4$). The solvent was removed in vacuo to leave a yellow oil (26.73 g). Purification by gravity chromatography (SiO2, 70-230 mesh; 5:1 - 4:1 hexane/ethyl acetate) gave the sub-titled cyano-ester as a slightly yellow oil (20.3 g, 79%). NMR (CDCl3-TMS) δ1.95-3.15 (m, 5, OOC-CH$(CH_2)_2$), 3.77 (s, 3, OCH3), 3.9-4.2 (m, 1, NC-CH), 7.1-7.6 (m, 4, aromatic H). IR =CH 3065, 3024, 3007; C-H 2953, 2848; CN 2241; C=O 1738; C=C 1605, 1584, 1497; C=C/CH def. 1452, 1437; C-O/other 1262, 1205, 1176; γCH 744. UV (Ethanol) 209 nm (E 8,500), 252 sh (258), 258 (293), 263 (310), 265 (312), 272 (276). Mass spec. m^+ at m/z 215.

Exact Mass Calcd. for $C_{13}H_{13}NO_2$: 215.0946. Found: 215.0954.

VPC Mass spec. (3% OV17,6',Programmed: Initial,125°C; temperature change +4°C per minute) shows peaks at 10 minutes (mass spec. m^+ at m/z 215) and 10.5 minutes (mass spec. m^+ at m/z 215). The compound is a mixture of diastereomers.

G. Preparation of cis- and trans-1,2,3,4-Tetrahydro-4-cyano-2-naphthalenecarboxamide:

The cyano ester (19.0 g, 0.883 mol) from part E hereinabove and saturated ammonia in methanol (300 mls) were stirred in a tightly stoppered flask for 48 hours, and the solvent was removed in vacuo. The compound was again dissolved in saturated ammonia in methanol (200 mls), and the mixture was stirred for 30 hours. The solvent was removed in vacuo to leave a yellow solid (17.82 g). A sample (5.0 g) was purified via low pressure column chromatography (SiO_2, 0.040-0.063 mm, 20% hexane/ethyl acetate to pure ethyl acetate) to give the trans isomer of the sub-titled compound (2.28 g) as a slightly yellow solid. A sample (0.5 g) was crystallized from chloroform to give colorless needles (0.41 g, mp 174-174°C). NMR ($CDCl_3$-TMS, 300 MHz) δ2.177-2.277 (8 lines (two dd); J=6.1 Hz by beta (eq) C_1, 11.3 Hz by alpha (ax) C_3, 13.7 Hz by alpha (eq) C_2; 1; beta (ax) C_2 H); 2.362-2.432 (12 lines,1,alpha (eq) C_2 H); 2.856-2.957 (14 lines,1,alpha (ax) C_3 H); 2.992, 3.012, 3.049, 3.069 (4 lines (dd); J=17.2 Hz by beta (ax) C_4, 5.9 Hz by alpha (ax) C3; 1; alpha (eq) C_4 H); 3.049, 3.084, 3.103, 3.140 (4 lines (dd); J=16.9 Hz by beta (ax) C_4, 10.7 Hz by alpha (ax) C_3; 1; beta (ax) C_4 H); 4.122, 4.134, 4.143, 4.154 (4 lines (dd); J=6.1 Hz by beta (ax) C_2, 3.4 Hz by alpha (eq) C_2; 1; beta (eq) C_1 H); 5.50-5.80 (br. d,2,NH_2); 7.14-7.33 (m,4,aromatic H). IR NH 3446, 3432, 3310, 3203; =CH 3083, 3070, 3020; CN 2235; C=O 1663; NH def. 1615 sh., 1612; C=C 1494; γCH/ other 761, 738. UV (Ethanol) 209 sh (E 8,900), 211 (8,900), 216 sl. sh. (7,300), 259 sh. (qualitative), 265.5 (308), 273 (292). Mass spec. m^+ at m/z 200.

Exact Mass Calcd. for $C_{12}H_{12}N_2O$: 200.0950. Found: 200.0937.

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.45; H, 6.04; N, 13.78.

A second band (1.43 g of a slightly yellow solid) was also obtained. A sample (0.40 g) was crystallized from chloroform to give the sub-titled cis-isomer as an off-white solid (0.38 g, mp 148.5-

150°C). NMR ($CDCl_3$-TMS, 300MHz) δ2.137, 2.180, 2.226, 2.266 (4 lines (q); J=12.3 Hz by beta (ax) C_1, 12.3 Hz by beta (eq) C_2, 12.3 Hz by beta (ax) C_3; 1; alpha (ax) C_2 H); 2.550-2.630 (m,2,beta (ax) C_3 H and beta (eq) C_2 H); 2.550-2.630 (m,2,beta (ax) C_3 H and beta (eq) C_2 H; 3.011 center (8 lines (ddd); J=16.1 Hz by alpha (ax) C_4, 5.7 Hz by beta (ax) C_3, 2.0 Hz by aromatic H; 1, beta (eq) C_4 H); 3.069, 3.106, 3.126, 3.163 (4 lines (dd); J=17.0 Hz by beta (eq) C_4, 11.2 Hz by beta (ax) C_3; 1; alpha (ax) C_4 H); 4.070, 4.090, 4.113, 4.129 (4 lines (dd); J=12.2 Hz by alpha (ax) C_2, 5.4 Hz by beta (eq) C_2; 1; beta (ax) Cl H); 5.55-5.70 (br. d,2,NH_2); 7.14 - 7.53 (m,4,aromatic H). IR NH 3431, 3310, 3272, 3197; -CH 3080, 3071, 3019; CN 2237; C=O 1667; NH def. 1630,1621; C=C 1579, 1493; γCH/other 772, 742. UV (Ethanol) 208 nm (E 8850), 211 (8800), 216 sh. (7450), 260 sh. (270), 264 (310), 265 (316), 273 (290), 290 sh. (14). Mass spec. m^+ at m/z 200.

Exact. Mass Calcd. for $C_{12}H_{12}N_2O$: 200.0950. Found: 200.0933.

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 70.98; H, 5.92; N, 13.79.

H. Preparation of Cis- and trans-3-amino-1,2,3,4-Tetrahydro-1-naphthalenecarbonitrile:

The carboxamide (13.21 g, 0.066 mol) from part F was dissolved in 1:1 acetonitrile/water (200 mls), and bis(trifluoroacetoxy)iodobenzene (34.00 g, 0.079 mol) was added. The mixture was stirred for 20 hours at room temperature, and the solvent was removed in vacuo. The residue was partitioned between 5% HCl and ether, and the aqueous solution was again washed with ether. The aqueous solution developed a precpitate which was washed with water and dried to give a yellow solid (0.64 g). The compound was boiled in methanol (30 mls) and filtered to remove a small amount of a yellow precipitate. The filtrate was concentrated on the steam bath until crystallization began, and ether was added to the point of cloudiness. The compound was allowed to crystallize at room temperature for 1 hour and at -10°C for 1 hour. The crystals were collected by filtration and washed with ether to give the sub-titled trans isomer compound as a colorless solid (0.55 g, mp 249-250°C). NMR (DMSO-d^6, TMS) δ1.9-3.75 (m,5,Ph-CH_2-CH-CH_2); 4.57, 4.61, 4.64, 4.68 (dd, J=3.5 Hz, 5.5 Hz,

1,NC-CH); 7.1-7.4 (m,4,aromatic H); 8.63 (br. s,3,NH^+). IR NH^+/=CH 3216, 3189, 3139, 3069; NH^+ 2740, 2729, 2714, 2687, 2598, 2563, 2545, 2485, 2015; CN 2241; C=C/NH^+ 1608, 1580, 1501; C=C/NH def. 1456; C-N/other 1113; γCH/ other 788, 751. UV (Ethanol) 209 nm (E 8,500), 253 sh. (280), 256 (294), 260 sh. (282), 263 (282), 264 sh. (273), 272 (219), 293 (23). Mass spec. m^+ for free base at m/z 172.

Exact Mass Calcd. for $C_{11}H_{12}N_2$: 172.1000. Found: 172.0982.

Anal. Calcd. for $C_{11}H_{12}N_2 \cdot HCl$: C, 63.31; H, 6.28; N, 13.42; Cl, 16.99. Found: C, 63.19; H, 6.38; N, 13.17; Cl, 17.07.

The aqueous filtrate was basified with 40% NaOH while cooling in ice. The free base was extracted three times with ether, and the extracts were washed with sat. NaCl and dried ($MgSO_4$). The solvent was removed in vacuo to leave a dark oil (7.41 g, 65% of a mixture of the cis and trans isomers of the sub-titled 3-amino-1-naphthene carbonitrile). NMR ($CDCl_3$-TMS) δ1.45 (br. s,2,NH_2), 1.6-3.7 (m,5,-Ph-CH_2-CH-CH_2), 3.9-4.25 (m,1,NC-CH), 7.0-7.55 (m,4,aromatic H).

I. Preparation of Cis-3-amino-1,2,3,4-tetrahydro-1-naphthalenecarbonitrile and its maleate salt:

The cis-carboxamide (0.87 g, 4.34 mmol) from part F hereinabove was dissolved in THF (25 mls), and distilled water (20 mls) was added. Bis(trifluoroacetoxy)iodobenzene (2.15 g, 5.0 mmol) was added, and the mixture was stirred for 4 hours. Bis(trifluoroacetoxy)iodobenzene (0.65 g, 1.5 mmol) was again added, and the mixture was stirred for a total of 2.5 days. Water (20 mls) and 10% HCl (10 mls) were added, and the solution was washed twice with ether. The aqueous solution was basified to pH 8-9 with concentrated ammonium hydroxide. The free base was extracted three times with ether, and the extracts were washed with sat. NaCl and dried ($MgSO_4$). The solvent was removed in vacuo to leave a light yellow oil (0.57 g). The resulting sub-titled 3-amino-1-naphthalenecarbonitrile compound was dissolved in ether, and a solution of maleic acid (0.40 g) in ether was added. The precipitate was filtered, washed with ether, and crystallized from methanol/ether to give the sub-titled maleate salt as a light-yellow solid (0.76 g, mp 174-175°C. NMR (DMSOd^6, TMS) δ1.77, 1.92, 2.07, 2.22 (4 lines,J=12 Hz,1,NC-C-CH); 2.4 - 3.8 (m,4);

4.53, 4.59, 4.67, 4.75 (dd,J=5.5 Hz and 11.9 Hz,1, NC-CH); 6.03 (s,2,maleic acid CH=CH); 7.18-7.43 (m,4,aromatic H); 7.3-8.5 (br. s,3,NH^+). IR NH^+/acid OH 3060, 2721, 2645, 2586, 2537; CN 2243; C=O 1694; C=C/NH^+ 1620; COO^- 1572, 1545 sh; COO^-/ C=C/NH^+ 1491-1485; C-O/other 1359, 1203, 1100; maleate 862; γCH/ other 779, 752. UV (Ethanol) 210 nm (E 25,050), 262 sl. sh. (780), 272 (525). Mass spec. m^+ at m/z 172.

Exact Mass Calcd. for $C_{11}H_{12}N_2$: 172.1000. Found: 172.0990.

Anal. Calcd. for $C_{11}H_{12}N_2 \cdot C_4H_4O_4$: C, 62.49; H, 5.59; N, 9.72; Found: C, 62.29; H, 5.53; N, 9.69.

J. Preparation of 3-(N,N-Dipropylamino)-1,2,3,4-tetrahydro-1-naphthalenecarbonitrile:

A mixture of the primary amine (As a mixture of the cis- and trans-isomers of the primary amine from part G hereinabove (2.77 g, 0.016 mol), n-propyl iodide (7.8 mls, 0.080 mol), potassium carbonate (11.13 g, 0.080 mol), and acetonitrile (150 mls) was stirred at reflux for 13.5 hours. The solvent was removed in vacuo, and the residue was partitioned between ether and water. The aqueous solution was extracted twice more with ether, and the combined organics were washed with Sat. NaCl and dried ($MgSO_4$). The solvent was removed in vacuo to leave the sub-titled N-N-dipropylamine compound as a yellow oil (2.94 g, 71%). NMR ($CDCl_3$-TMS) δ0.89 (t,J=7.2 Hz,6, N-C-C-CH_3), 1.15-1.70 (m,4,N-C-CH_2), 2.3-2.57 (m,4,N-CH_2), 1.75-3.5 (m,5,Ph-CH_2-CH-CH_2), 3.8-4.25 (m,1,NC-CH), 7.0-7.55 (m,4,aromatic H). IR =CH 3065, 3022; CH 2960, 2934, 2872; N-C-H 2813; CN 2238; C=C 1583, 1496; γCH 743. UV (Ethanol) End Abs., 251 nm (E 449), 258 (444), 265 (474), 273 (428), 293 (126), 306 sh. (95), 313 sl. sh. (77), 321 (64). Mass spec. m^+ at m/z 256.

Exact Mass Calcd. for $C_{17}H_{24}N_2$: 256.1939. Found: 256.1942.

K. Reduction of the nitrile:

Preparation of 3-(N,N-dipropylamino)-1,2,3,4-tetrahydro-1-naphthalenylmethylamine:

Sulfuric acid (100%, 3.87 g, 0.0395 mol) was added dropwise to a stirred suspension of lithium aluminum hydride (3.0 g, 0.079 mol) in THF (150 mls). A solution of the sub-titled naphthalenecarbonitrile (2.67 g, 0.0104 mol) from part I hereinabove in THF (100 mls) was

added dropwise to the resulting aluminum hydride at 0°C, and the mixture was stirred at that temperature for 3 hours. Water (3 mls), 15% NaOH (3 mls), and water (9 mls) were added in succession, and the aluminum salts were filtered and washed well with ether. The filtrate was dried ($MgSO_4$), and the solvent was removed in vacuo to leave the sub-titled-1-naphthalenemethylamine as a yellow oil (2.67 g, 99%). NMR ($CDCl_3$-TMS) δ0.88 (t,J=7.1 Hz,6,N-C-C-CH_3); 1.2-1.65 (m,6, N-C-CH_2 and NH_2); 2.39, 2.46, 2.49, 2.59 (dd, J=6.2 Hz and 8.4 Hz,4,tertiary N-CH_2); 1.2-3.15 (m,8,other aliphatic protons); 6.9-7.3 (m,4,aromatic H). IR NH 3373, 3288, 3185; =CH 3061, 3017; CH 2958, 2932, 2872, 2809; NH def./C=C 1660, 1642 sh., 1604, 1580, 1490; CH def. 1451; C-N/other 1070; γCH/other 742. Mass spec. m^+ at m/z 260.

Exact Mass Calcd. for $C_{17}H_{28}N_2$: 260.2252. Found: 260.2250.

L. Preparation of the N-formyl compound:

Preparation of 3-(N,N-dipropylamino)-1,2,3,4-tetrahydro-1-naphthalenylformamide:

The sub-titled-methylamine (2.60 g, 0.010 mol) from part J hereinabove was dissolved in ethyl formate (50 mls), and the solution was refluxed for 18.5 hours. The solvent was removed in vacuo to leave an oil (3.2 g). The compound was purified via gravity chromatography (SiO_2; 5% CH_3OH, 0.5% NH_3, $CHCl_3$) to give the sub-titled-1-naphthalenylformide as an oil (2.07 g, 72%). NMR ($CHCl_3$-TMS) δ0.88 (t, J=7.0 Hz, 6, N-C-C-CH_3); 1.15-1.75 (m,4,N-C-CH_2); 2.38, 2.47, 2.45, 2.56 (dd, J=6.8 Hz and 7.7 Hz,4,tertiary N-CH^1); 1.75-4.1 (m,8,aliphatic H); 5.5-6.1 (m,1,NH); 7.0-7.3 (m,4,aromatic H); 7.9-8.27 (m,1,CHO). IR NH 3377; =CH/NH 3060, 3020; CH 2958, 2933, 2872; N-C-H 2812; C=O 1664; C=C 1607, 1579, 1491; amide II 1538; CH def./C=C/-other 1451, 1384; C-N/other 1245, 1231, 1070; γCH 745. UV (Ethanol) 212 nm sl. sh. (E 12,900), 253 sh. (303), 260 sh. (387), 266 (502), 273 (485). Mass spec.: No m^+; [m^+ - CHO] or [m^+ - C2H5] at m/z 259.

M. Preparation of the N-formyl compound:

Preparation of 3-(N,N-dipropylamino)-1,2,3,4-tetrahydro-1-naphthalenylformamide (alternate method):

A mixture of formic acid (95%, 2.7 g, 0.055 mol) and acetic anhydride (5.3 g, 0.052 mol) was stirred at room temperature for 3 hours. The mixture was cooled in ice, a solution of the primary

amine from step J hereinabove (9.59 g, 0.0368 mol) in THF (30 mls) was added over a 30 minute period, and the reaction was stirred at 0°C for 1 hour and at room temperature for 2 hours. The mixture was diluted with water (300 mls) and 10% HCl (25 mls), washed twice with ether, and basified with 40% NaOH while cooling in ice. The milky mixture was extracted twice with ether, and the extracts were washed with sat. NaCl and dried ($MgSO_4$). The solvent was removed in vacuo to leave an amber oil (9.23 g, 87%). The compound was the same by NMR as that prepared using ethyl formate.

N. Preparation of 3,3a,5,6-Tetrahydro-N,N-dipropyl-4H-Benz-[de]isoquinolin-5-amine:

A mixture of the sub-titled formamide (0.50 g, 1.73 mmol) from parts K or L hereinabove and polyphosphoric acid (7 g) was heated with stirring in an oil bath maintained at 160°C for 4 hours to cyclize the compounds. The reaction mixture was dissolved in water, basified with 40% NaOH, and extracted three times with ether. The extracts were washed with sat. NaCl and dried ($MgSO_4$). The solvent was removed in vacuo to leave the hereinabove sub-titled unsaturated N-ring-benz-isoquinolin-5-amino compound as a brown oil (0.34 g, 73%). NMR ($CDCl_3$-TMS) δ0.83, 0.88 (d of t, J=7.2 Hz,6,N-C-C-CH_3); 1.1-1.7 (m,6,N-C-CH_2/other); 1.75-2.3 (m,-2); 2.39, 2.46, 2.49, 2.57 (dd, J=6.1 Hz and 8.5 Hz, 4, tertiary N-CH_2); 2.65-3.3 (m,-4); 3.7 - 4.2 (m,-1); 7.0-7.35 (m,4,aromatic H); 8.32 (br. s,1,N=CH). Mass spec. m^+ at m/z 270.

Exact Mass Calcd. for $C_{18}H_{26}N_2$: 270.2096. Found: 270.2091.

When the reaction was repeated using the formamide (3.88 g, 0.0135 mol) and polyphosphoric acid (56 g), a brown oil (3.53 g, 97%) was obtained. Purification by low pressure column chromatography (SiO_2, 0.040-0.063 mm; 2% CH_3OH, 0.2% NH_3, $CHCl_3$) gave two isomers of the cyclized material and a band consisting of a mixture of the two isomers (1.53 g). Isomer 1 weighed 0.50 g. NMR ($CDCl_3$-TMS) δ0.83 (t,J=7.1 Hz,6,N-C-C-CH_3); 1.15-1.65 (m,6,lines,4,N-C-CH_2); 1.7-2.35 (m,2); 2.39, 2.46, 2.49, 2.58 (dd, J=6.1 Hz and 8.8 Hz,4,teriary N-CH_2); 2.7-3.35 (m,5); 3.9-4.1 (m,1); 7.0-7.3 (m,3,aromatic H); 8.25-8.4 (m,1,N=CH). Isomer 2 weighed 0.70 g. NMR ($CDCl_3$-TMS) δ0.89 (t,J=7.0 Hz,6,N-C-C-CH_3); 1.2-1.7 (m,6 lines,4,N-C-CH_2); 1.7-2.25

(m,2); 2.39, 2.46, 2.49, 2.57 (dd, J=6.2 Hz and 8.4 Hz,4,tertiary N-CH_2); 2.6-3.3 (m,5); 3.9-4.18 (m,1); 7.0-7.3 (m,3,aromatic H); 8.25-8.37 (m,1,N=CH).

O. Preparation of 2,3,3a,4,5,6-Hexahydro-N,N-dipropyl-1H-Benz-[de]isoquinoline-5-amine, (E)-2-butenedioate (2:3), hydrate (1:1) (Isomer 1):

Sulfuric acid (100%,1.29 g, 0.0132 mol) was added dropwise to an ice cooled suspension of lithium aluminum hydride (1.0 g, 0.0263 mol) in THF (50 mls) with stirring. A solution of the tetrahydro unsaturated N-ring compound from part M hereinabove (Isomer 1, 0.50 g, 1.85 mmol) in THF (50 mls) was added over a 1 minute period, and the mixture was stirred for 15 minutes. Water (1 ml), 15% NaOH (1 ml), and water (3 mls) were added in succession, and the suspension was filtered. The aluminum salts were washed well with ether, and the combined filtrate was dried ($MgSO_4$). The solvent was removed in vacuo to leave a yellow oil (0.60 g). The sub-titled hexahydro (saturated N-ring) compound was mixed with fumaric acid (0.51 g), and the mixture was crystallized twice from ethanol/ether to give the sub-titled amine fumarate salt compound as a colorless solid (0.40 g, 47%; mp shrinks 150-158°C, melts 158-165°C with evolution of gas). NMR (DMSO-d^6,TMS) δ0.85 (t,J=7.0 Hz,6,N-C-C-CH_3), 1.1-1.7 (m,6 lines,4,N-C-CH_2), 1.8-2.2 (m,1), 2.25-3.3 (m,10), 3.3 - 3.6 (m,1), 4.19 (s,2,-N-CH_2-Ar), 4.38 (br. s,NH^+ and OH), 6.50 (s,3,fumarate CH=CH), 6.85-7.3 (m,3,aromatic H). IR water OH 3402; NH+/acid OH 2723, 2611, 2508, 2272; C=O 1714; C=C/COO- 1639, 1567; C-O/C-N/other 1283, 1248, 1174; other 975. UV (Ethanol) 210 nm sl. sh. (E 29,050). Mass spec. m^+ for free base at m/z 272.

Exact Mass Calcd. for $C_{18}H_{28}N_2$: 272.2252. Found: 272.2251.

Anal. Calcd. for $C_{18}H_{28}N_2 \cdot 1.5\ C_4H_4O_4 \cdot H_2O$: C, 62.05; H, 7.81; N, 6.03. Found: C, 62.38; H, 7.48; N, 5.98.

P. Preparation of 2,3,3a,4,5,6-Hexahydro-N,N-dipropyl-1H-Benz[de]isoquinoline-5-amine, (E)-2-butenedioate (2:3), hydrate (2:1) (Isomer 2):

The N-ring saturating reaction was run in a manner similar to that in part N hereinabove for the preparation of the product of part N, hereinabove using sulfuric acid (100%, 1.29 g, 0.0132 mol), lith-

ium aluminum hydride (1.00 g, 0.0263 mol; in 50 mls of THF), and the tetrahydroisoquinoline (Isomer 2, 0.05 g, 1.85 mmol; in 40 mls of THF). A yellow oil (0.40 g) was obtained. The resulting sub-titled N-ring saturated compound was mixed with fumaric acid (0.19 g) and crystallized twice from ethanol/ether to give tan-brown clusters of the herein sub-titled amine (0.34 g; mp 110-111°C with an evolution of gas). NMR (DMSO-d^6, TMS) δ0.84 (t,J= 7.0 Hz,6,N-C-C-CH_3), 1.15-1.7 (m,6 lines,4, N-C-CH_2), 1.8-2.2 (m,1), 2.3-3.35 (m,10), 3.35-3.67 (m,1), 4.16 (s,2,N-CH_2-Ar), 6.47 (br. s,NH^+ and OH), 6.47 (s,fumarate CH=CH), 6.9-7.22 (m,3,aromatic H). IR OH/NH 3449, 3250; NH^+/acid OH 2729, 2645, 2516, 2258; C=O 1699; C=C/COO^- 1624, 1567; C-O/C-N 1289-1273, 1230, 1191; other 997, 985, 810; γCH/other 753. UV (Ethanol) 210 nm sl. sh. (E 26,200). Mass spec. m^+ for free base at m/z 272.

Exact Mass Calcd. for $C_{18}H_{28}N_2$: 272.2252. Found: 272.2248.

Anal. Calcd. for $C_{18}H_{28}N_2 \cdot 1.5\ C_4H_4O_4 \cdot 0.5\ H_2O$: C, 63.28; H, 7.74; N, 6.15. Found: C, 63.85; H, 8.27; N, 6.04.

Q. Preparation of 5,6-Dihydro-N,N-dipropyl-4H-Benz[de]isoquinolin-5-amine (E)-2-butenedioate (2:3) and 8,9-Dihydro-N,N-dipropyl-7H-Benz[de]isoquinolin-5-amine (E)-2-butenedioate (1:1):

A mixture of the dihydro N-ring unsaturated compound from part M hereinabove (3.86 g, 0.0143 mol), 10% palladium on carbon catalyst (2.0 g), and decalin (50 mls) was stirred at reflux in an oil bath maintained at 210°C for 1.8 hours, and the mixture was filtered through a filter aid (Celite™). The palladium catalyst was washed with ether, and the filtrate was extracted twice with 20 mls of 10% HCl. The extracts were washed with ether and basified with 40% NaOH. The free base was extracted three times with ether, and the extracts were washed with sat NaCl and dried ($MgSO_4$). The solvent was removed in vacuo to leave a a brown oil (2.52 g). Purification by gravity chromatography (SiO_2, 1% CH_3OH, 0.1% NH_3, $CHCl_3$) gave two bands. The first yellow band was collected and the solvent was removed in vacuo to leave a brown oil (1.18 g). The compound was dissolved in ether and filtered to remove an insoluble material. The filtrate was evaporated to dryness to leave the titled saturated N-ring amine compound as a brown oil (0.88 g). Fumaric acid (0.39 g) was added, and the mixture was crystallized from methanol/ether to give the fumarate

salt as a yellow-orange solid (U-71494E; 0.90 g; mp 167°C dec). δ0.92 (t,J=7.2 Hz,6,N-C-C-CH_3); 1.3-1.8 (m,6 lines,4,N-C-CH_2); 1.82.-1 (m,5 lines,1,aromatic-C-CH_2); 2.75-3.1 (m,4,lines,4,aromatic-CH_2); 3.35 (br. t, J=7.4 Hz,4,N-CH_2); 4.6-5.1 (br. s,NH^+); 6.64 (s,2,fumarate CH=CH); 6.79, 6.82 (d,J=2.3 Hz,1,C-4 aromatic H); 7.02-7.15 (m,1,C-6 aromatic H); 7.90 (s,1, C-1 aromatic H); 8.81 (s,1,C-3 aromatic H). IR =CH 3065; NH^+/ COOH 2585, 2508, 2154; C=O 1686; C=C/C=N/COO^- 1637, 1607, 1530, 1509; C-O/C-N/other 1264, 1247, 1208; γCH/other 985; γCH 879, 804, 795. UV (Ethanol) 212 nm (E 35,050), 251 (25,600), 273 (21,650), 294 (16,000), 307 (17,450), 388 (2,400). Mass spec. m^+ for free base at m/z 268.

Exact Mass Calcd. for $C_{18}H_{24}N_2$: 268.1939. Found: 268.1927.

Anal. Calcd. for $C_{18}H_{24}N_2 \cdot C_4H_4O_4$: C, 68.73; H, 7.34; N, 7.29. Found: C, 68.18; H, 7.36; N, 7.16.

The second band gave a brown oil (0.60 g). The compound was dissolved in ether and filtered to remove an insoluble precipitate. The filtrate was evaporated to dryness to leave a brown oil (0.59 g). Fumaric acid (0.26 g) was added, and the mixture was crystallized from methanol/ether to give the sub-titled 1.5 molar proportion fumarate salt as a tan solid (U-71495E; 0.59 g; mp 165-166°C with an evolution of gas). NMR (DMSO-d^6, TMS) δ0.88 (t,J=7.0 Hz,6,N-C-C-CH_3), 1.2-1.75 (m,6 lines,4,N-C-CH_2), 2.72 (def t,7.2 Hz,4,N-CH_2), 3.0-3.35 (m,5,N-$CH(CH_2)_2$), 5.2-6.0 (br. s,1-2,NH^+), 6.61 (s,3,Fumarate CH=CH), 7.45-7.55 (m,2,aromatic H), 7.77-8.0 (m,1,aromatic H), 8.33 (s,1,C-3 aromatic H), 9.12 (s,1,C-1 aromatic H). IR NH^+/COOH 2452, 1952, 1890; C=O 1698; C=C/C=N/COO^- 1639, 1603; C-O/C-N/other 1340, 1263, 1184; γCH/other 989, 978, 879, 768. UV (Ethanol) 221 nm (E 57,950), 268 sh. (4,100), 278 (4,800), 288 (4,550), 314 (3,350), 323 sh. (3,400), 327 (4,350). Mass spec. m^+ for free base at m/z 268.

Exact Mass Calcd. for $C_{18}H_{24}N_2$: 268.1939. Found: 268.1940.

Anal. Calcd. for $C_{18}H_{24}N_2 \cdot 1.5\ C_4H_4O_4$: C, 65.08; H, 6.82; N, 6.31. Found: C, 65.06; H,6.91; N, 6.23.

Example 2 — 3aS-Trans-5-(Dipropylamino)-3a,4,5,6-Tetrahydro-1H-Benzo[de]quinolin-2(3H)-one, Mono(4-Methylbenzenesulfonate) (U-72717E) and 3aS-Trans-5-(Dipropylamino)-

3a,4,5,6-Tetrahydro-1-propyl-1H-benzo[de]quinolin-2(3H)-one, hydrochloride, hydrate (1:1:0.8):

A. Preparation of 3-Carboxy-1,2,3,4-Tetrahydro-1-Naphthaleneacetic Acid:

The ketone, 3-(methoxycarbonyl)-1(2H,4H)naphthalenone, (5.0 g, 0.0245 mol) was dissolved in ether (50 mls) and benzene (100 mls), and activated zinc dust (9.61 g, 0.147 mol) and a few crystals of iodine were added. The mixture was brought to reflux, and ethyl bromoacetate (8.2 g, 0.049 mol) in benzene (10 mls) was added dropwise over a 15 minute period. The mixture was refluxed for 1 hour, diluted with ether, washed 3 times with 10% HCl and once with sat. NaCl, and dried ($MgSO_4$). The solvent was removed in vacuo to leave a yellow oil (6.7 g). NMR ($CDCl_3$-TMS) shows ethyl ester at δ1.25 (t, J=7.1 Hz) and a doublet of quartet at 4.0-4.35; the methyl ester was partially absent. The compound was dissolved in acetic acid (75 mls), 10% palladium on carbon (1 g) and 70% perchloric acid (1 ml) were added, and the mixture was hydrogenated in a Parr apparatus for 18 hours. The product mixture was filtered through a (Celite™) filter aid and the filtrate was evaporated to dryness in vacuo. The brown oil was refluxed in a mixture of methanol (20 mls) and 15% NaOH (75 mls) for 3 hours, and the solution was washed twice with ether. The solution was acidified with conc. HCl while cooling in ice. The precipitate was filtered, washed with water, and dried in vacuo at 80°C to give the sub-titled diacid; 4.21 g, 73.5%; mp 202-207 °C). NMR ($CDCl_3$, CD_3OD, TMS) δ1.37, 1.51, 1.67, 1.81 [4 lines (q), J=12 Hz,1,C_3 axial H]; 2.2-3.6 (m,7); 7.0-7.3 (m,3,aromatic H). IR =CH/-Acid OH 3023; Acid OH 2729, 2664; C=O 1700; C=C 1604, 1580, 1494, 1454; C-O 1285, 1194; Acid OH 936; γCH 753. UV (Ethanol) 209 nm sh, (E 9,280), 217 sl. sh. (7,650), 253 sl. sh. (246), 260 sh. (342), 266 (447), 273 (445), 290 sl. sh. (45). Mass spec. m^+ at m/z 234.

Exact. Mass Calcd. for $C_{13}H_{14}O_4$: 234.0892. Found: 234.0899.

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.66; H, 6.16.

B. Preparation 1,2,2a,3,4,5-hexahydro-1-oxo-4-acenaphthylenecarboxylic acid:

A mixture of the diacid from part A hereinabove (3.40 g, 0.0145

mol) and thionyl chloride (11.25 g, 0.0946 mol) in benzene (70 mls) was stirred at reflux for 4.5 hours during which time the acid slowly reacted and went into solution. The solvent was removed in vacuo, benzene (25 mls) was added, and the solvent was again removed in vacuo. This was repeated twice with 40 mls of methylene chloride leaving a brown oil. The compound was dissolved in methylene chloride (70 mls), and the solution was cooled to -78°C. Trifluoromethanesulfonic acid (4.41 g, 0.0294 mol) was added, and the mixture was allowed to warm to 0°C with stirring overnight. The mixture was washed twice with 70 mls of water, and the washings were back extracted with ether. The combined organics were dried ($MgSO_4$), and the solvent was removed in vacuo to leave a blue-green solid. Sodium hydroxide (5%, 100 mls) was added, and the mixture was shaken until the compound dissolved. The solution was washed with ether and filtered. The filtrate was acidified with conc. HCl, and the mixture was cooled in ice for 30 minutes and the ppt was filtered. The ppt was washed twice with water and dried in vacuo to leave a yellow brown solid (2.55 g, 81%). A sample (0.55 g) was crystallized from acetonitrile to give the sub-titled compound as a brown solid, (0.44 g, mp 207-209°C). NMR (DMSO-d^6, TMS) δ1.05-1.65 (m,1), 2.15-3.5 (m,7), 7.0-7.55 (m,3,aromatic H). IR Acid OH 3145; =CH 3067; 3019; Acid C=O 1732; Ketone C=O 1681; C=C 1593; C-O/other 1272, 1248, 1216, 1177, 1159; γCH/other 849, 799, 753. UV (Ethanol) 210 nm (E 23,420), 252 (16,800), 299 (2,890). Mass spec. m^+ at m/z 216.

Exact Mass Calcd. for $C_{13}H_{12}O_3$: 216.0786. Found: 216.0778.

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.00; H, 5.72.

C. Preparation of (2,3,3a,4,5,6-Hexahydro-2-oxo-1H-benzo[de]-quinolin-5-yl)carboxylic acid:

The sub-titled ketone (1.51 g, 7.0 mmol) from part B hereinabove was stirred in methanesulfonic acid (15 mls) at 0°C until the compound dissolved (-10 min). Sodium azide (0.68 g, 0.0105 mol) was added portionwise over a 40 minute period at 0°C, and the reaction mixture was stirred at 10°C for two hours. The product mixture was poured onto 50 mls of crushed ice, and the aqueous suspension was stirred for 10 minutes and filtered. The precipitate was washed

several times with water and dried in vacuo at 60°C overnight leaving the sub-titled benzo-quinolin-5-ylcarboxyli acid as a tan solid (1.32 g, 82%). NMR (DMSO-d^6, TMS) δ1.13, 1.28, 1.42, 1.56 (m 4 lines, 1,N(C=O)-C-C-CH); 1.9-3.5 (m,7); 6.62, 6.73 (d,J=7.5 Hz,1,C-7 or C-9 aromatic H); 6.63, 6.80 (d,J=6.4 Hz,1,C-7 or C-9 aromatic H); 6.96, 7.06, 7.15 (dd,J=7.3 Hz and 7.6 Hz,1,C-8 aromatic H); 10.02 (s,1,lactam NH). IR NH/=CH/acid OH 3198, 3132, 3066, 3044; Acid OH 2800-2600 (broad); Acid C=O 1725; Lactam C=O 1652; C=C 1615, 1592; C-O/C-N/other 1255, 1241, 1210, 1201, 1181; γCH/other 785, 736. UV (Ethanol) 210 nm (E 25,760), 252 (9,210), 278 sl. sh. (1,960), 285 sh. (1,390). Mass spec. m^+ at m/z 231.

D. Preparation of 3aS-trans-(2,3,3a,4,5,6-hexahydro-2-oxo-1H-benzo[de]quinolin-5-yl)carbamic acid, 1,1-dimethylethyl ester, (the part D urethane):

A mixture of the benzo-quinolin-5-ylcarboxylic acid from part C hereinabove (1.25 g, 5.41 mmol), diphenylphosphoryl azide (1.55 g, 5.61 mmol), triethylamine (0.83 mls, 5.95 mmol), and t-butanol (distilled from potassium t-butoxide, 50 mls) was stirred at reflux for 22 hours. The solvent was removed in vacuo, and the residue was dissolved in 5:1 CH_2Cl_2/THF. The organic solution was washed twice with 15% NaOH, and the washings were back extracted with CH_2Cl_2. The combined organics were dried ($MgSO_4$), and the solvent was removed in vacuo to leave a yellow-brown foam (1.43 g). Purification by low pressure column chromatography (SiO_2, 0.040-0.063 mm; 50% hexane/-ethyl acetate to 10% hexane/ethyl acetate) gave a white solid (0.75 g, 46%). A sample was crystallized from methylene chloride to give the sub-titled carbamate ester as a colorless solid (mp 187-189°C). NMR ($CDCl_3$-TMS, 300 MHz) δ1.253, 1.294, 1.335, 1,376 [4 lines (q); J=12.2 Hz by beta (eq) c-4, 12.2 Hz by beta (ax) C-3a, 12.2 Hz by beta (ax); 1; C-5 (N-CH)]; 1.407 (s, 9,t-butyl); 2.055, 2.094 [br. d, J=11.8 Hz,1, beta (eq) C-4 H]; 2.146, 2.196, 2.248 [3 lines (t); J=15.4 Hz by beta (eq) C-3, 15.4 Hz by beta(ax) C-3a; 1; alpha (ax) C-3 H]; 2.374, 2.391, 2.427, 2.446 [4 lines (dd); J=15.9 Hz by alpha (ax) C-3, 5.2 Hz by beta (ax) C-4; 1; beta (eq) C-3 H]; 2.541, 2.582, 2.597, 2.636 [4 lines (dd); J=16.5 Hz by beta (eq) C-6, 12.0 Hz by beta(ax) C-5; 1; alpha (ax) C-6 H]; 2.895, 2.911, 2.950, 2.966 [4

lines (dd); J=16.6 Hz by alpha (ax) C-6, 4.9 Hz by beta (ax) C-5 (N-CH); 1; beta (eq) C-6 H]; 3.03 center (m,1,beta C-3a H); 3.60-3.77 [m,1,beta (ax) N-CH]; 6.670, 6.698, 6.729 [3 lines (dd); J=7.8 Hz and 7.8 Hz; 2, aromatic C-7 and C-9 H]; 7.015, 7.042, 7.068 [3 lines (t),J=7.9 Hz,1,aromatic C-8 H]; 10.069 (s,1,amide NH). IR NH 3377, 3356, 3211, 3184; NH/=CH 3112, 3078, 3042; C=O 1698, 1687, 1679; C=C 1613, 1594; Amide II 1524; C-O/C-N/other 1317, 1175; CH def./other 784, 775, 736, 727. UV (Ethanol) 212 nm (E 29,000), 252 (11,700), 286 sh. (1,400). Mass spec. m^+ at m/z 302.

Anal. Calcd. for $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33; N, 9.26.

Found: C, 67.29; H, 7.27; N, 9.12.

E. Preparation of 3aS-Trans-5-amino-3a,4,5,6-tetrahydro-1H-benzo[de]quinolin-2(3H)-one and its monohydrochloride (U-72715A):

Trifluoroacetic acid (3.0 mls) was added to the part D urethane (0.44 g, 1.46 mmol), and the mixture was stirred in ice for 15 minutes to remove the tert-butoxy carbonyl group from the nitrogen. Excess etheral HCl was added to the sub-titled amine and the solvent was removed in vacuo to leave the sub-titled amine hydrochloride salt as a tan solid. The salt compound was boiled in methanol (25 mls; a solution was not achieved) and ether was added. The crystals were collected to give an off-white solid (U-72715A; 0.22 g, 63%; mp > 350°C). NMR (DMSO-d^6,TMS) δ1.25-1.8 (m,4 lines,1); 2.0-3.7 (m,7); 6.68, 6.78 (d, J=7.5 Hz,1,C-7 or C-9 aromatic H); 6.72, 6.81 (d, J=7.5 Hz,1, C-7 or C-9 aromatic H); 7.00, 7.10, 7.19 (dd,J=7.5 Hz and 7.5 Hz,1,C-8 aromatic H); 8.44 (br. s,3,NH^+); 10.10 (s,1,lactam NH). IR NH 3246; NH^+/=CH/NH 3084, 3035, 3015; NH^+ 2750, 2619, 2534, 2061; C=O 1674; C=C/NH^+ 1627, 1613, 1592, 1520, 1500; CH def/ other 797, 790, 743. UV (Ethanol) 211 nm (E 27,600), 253 (11,700), 287 sh. (1,350). Mass spec. m^+ for free base at m/z 202.

Exact Mass Calcd. for $C_{12}H_{14}N_2O$: 202.1106. Found 202.1101.

Anal. Calcd. for $C_{12}H_{14}N_2O \cdot HCl$: C, 60.38; H, 6.33; N, 11.73; Cl, 14.85. Found: C, 60.11; H, 6.49; N, 11.38; Cl, 14.44.

F. Preparation of 3aS-Trans-5-(Dimethylamino)-3a,4,5,6-Tetrahydro-1H-Benzo[de]quinolin-2(3H)-one, and its Monohydrochloride (U-73076A):

The sub-titled primary amine (U-72715A; 0.60 g, 2.5 mmol) from

part E hereinabove was dissolved in distilled water (25 mls) with warming, and absolute ethanol (100 mls), 37% aqueous formaldehyde (5.0 mls, ~62 mmol), and 10% palladium on carbon catalyst (0.50 g) were added. The mixture was hydrogenated in a Parr apparatus for 17 hours with an initial hydrogen pressure of 50 psi. The mixture was filtered through (Celite™) a filter aid and the catalyst was washed with methanol. The filtrate was evaporated to dryness to leave a white solid. The solid compound was dissolved in warm water (150 mls) and 10% HCl (10 mls), and the solution was washed with ether and filtered. The filtrate was basified with 40% NaOH, and the clear solution was extracted three times with ether and twice with methylene chloride. The extracts were washed with sat. NaCl, dried ($MgSO_4$), and the solvent was removed in vacuo to leave an oil (0.52 g). The compound was dissolved in a mixture of ether and methylene chloride and excess ethereal HCl was added. The ppt was washed with ether and crystallized from methanol (containing a small amount of water)/ether to give the sub-titled dimethylamine hydrochloride as a colorless solid (U-73076A; 0.43 g, 64%; mp 333°C dec.). NMR (DMSO-d^6,TMS) δ1.34, 1.51, 1.66, 1.81 (4 lines,J=11.8 Hz,1,NC-C-CH); 2.78 (s,6,NCH_3); 2.2-3.4 (m,6); 3.4-3.8 (m,1,N-CH); 6.69, 6.79 (d,J=7.8 Hz,1,C-7 or C-9 aromatic H); 6.74, 6.82 (d,J=6.7 Hz,1,C-7 or C-9 aromatic H); 7.03, 7.12, 7.22 (dd,J=7.6 Hz and 7.6 Hz,1,C-8 aromatic H); 10.14 (s,1,lactam NH). IR NH 3209, 3151, 3083; =CH 3040, 3008; NH^+ 2629, 2571, 2526, 2475; C=O 1675; C=C 1613, 1594, 1515, 1496, 1477; CH def. 1365, 1345; γCH/other 787, 742, 723. UV (Ethanol) 212 nm (E 27,300), 252 (11,700), 287 (1,350). Mass spec. m^+ for free base at m/z 230.

Exact Mass Calcd. for $C_{14}H_{18}N_2O$: 230.1419. Found: 230.1428.

Anal. Calcd. for $C_{14}H_{18}N_2O \cdot HCl$: C, 63.03; H, 7.18; N, 10.50; Cl, 13.29. Found: C, 62.75; H, 7.17; N, 10.42; Cl, 13.24.

C. Preparation of 3aS-Trans-5-(Dipropylamino)-3a,4,5,6-Tetrahydro-1H-Benzo[de]quinolin-2(3H)-one, Mono(4-Methylbenzenesulfonate) (U-72717E) and 3aS-Trans-5-(Dipropylamino)-3a,4,5,6-Tetrahydro-1-Propyl-1H-Benzo[de]quinolin-2(3H)-one, hydrochloride, hydrate (1:1:0.8):

A mixture of the primary amine (0.50 g, 2.47 mmol) from part E

hereinabove, 1-bromopropane (2.74 g, 0.0222 mol), 1-iodopropane (0.42 g, 2.47 mmol), and potassium carbonate (1.4 g, 0.010 mol) in acetonitrile (20 mls) was stirred at reflux in an oil bath for 18 hours. Additional quantities of 1-bromopropane (2.74 g) and potassium carbonate (1.4 g) were added, and the reflux was continued for a total of 41 hours. The mixture was diluted with ether and washed with water. The washings were back extracted with ether, and the combined organics were washed with sat. NaCl and dried ($MgSO_4$). The solvent was removed in vacuo to leave a yellow semisolid (0.68 g). Purification via gravity chromatography (SiO_2, 70-230 mesh; 2% methanol, 0.2% ammonia, chloroform) gave two bands: The first band (Rf=0.27, 0.21 g of a solid) was dissolved in ether and excess ethereal HCl was added. The mixture was cooled to -10°C for 2 hours, and the precipitate was filtered, washed with ether, and crystallized from ethanol/ether to give the N,N,N-tripropyl amino compound as an off-white solid (0.24 g, mp 207.5-208.5°C). NMR (DMSO-d^6,TMS) δ0.75, 0.85, 0.93 (t,J=7.0 Hz,3,Amide-C-C-CH_3); 0.85, 0.93, 1.02 (t,J=6.8 Hz,6,N-C-C-CH_3); 1.2-2.0 (m,7,N-C-CH_2/other); 2.2-3.4 (m,N-CH_2other); 3.5-4.1 (m,2,N-CH and O=C-C-CH); 6.84, 6.94 (d, J=7.7 Hz,1,C-7 or C-9 aromatic H); 6.94, 7.04 (d,J=8.1 Hz,1,C-7 or C-9 aromatic H); 7.15, 7.24, 7.34 (dd,J=7.6 Hz and 7.8 Hz,1, C-8 aromatic H); 10.88 (br. s,1,NH^+). IR OH/NH 3671, 3568, 3423, 3322; NH^+ 2609, 2511, 2456, 2425; C=O 1664; C=C 1601, 1588; C-N/ other 1311, 1294, 1238, 1149; γCH/other 777, 736. UV (Ethanol) 212 nm (E 29,225), 255 (11,300). Mass spec. M^+ for free base at m/z 328.

Exact. Mass Calcd. for $C_{21}H_{32}N_2O$: 328.2514. Found: 328.2505.

Anal. Calcd. for $C_{21}H_{32}N_2O \cdot 0.8\ H_2O$: C, 66.42; H, 9.19; N, 7.38; Cl, 9.34. Found: C, 66.43; H, 8.89; N, 7.42; Cl, 9.61.

The second band (Rf=0.13, 0.22 g of a solid) was dissolved in ether, and a solution of p-toluenesulfonic acid monohydrate (0.29 g) in ether was added. The mixture was cooled at -10°C for two hours and the precipitate was filtered. The compound was crystallized from methanol/ether to give the N,N-dipropylamine compound as an off-white solid (U-72717E, 0.35 g, mp 261-262°C). NMR (DMSO-d^6, TMS) δ0.83, 0.93, 1.01 (t, J=7.2 Hz,6,N-C-C-CH_3); 1.35-1.9 (m,5,N-C-CH_2/ other); 2.28 (s,3,tosyl CH_3), 2.2-2.6 (m,2); 2.8-3.3 (m,5,N-CH_2/other); 3.5-

4.0 (m,1,N-CH); 6.69, 6.78 (d,J=7.6 Hz,1,C-7 or C-9 aromatic H); 6.75, 6.83 (d,J=6.6 Hz,1,C-7 or C-9 aromatic H); 7.04, 7.14, 7.22 (m, 3 lines,3,C-8 aromatic H and tosyl A_2 of A_2B_2); 7.43, 7.53 (B_2 of A_2B_2,J=8.1 Hz,2,tosyl H); 8.97 (br. s, 1,NH^+); 10.12 (s,1,amide NH). IR NH 3226, NH/=CH 3173, 3105; NH^+ 2759, 2679, 2554; C=O 1677; C=C 1611, 1590; SO_3- 1165, 1034, 1012, 681; SO_3-/C-N/other 1231, 1119; γCH 823, 801. UV (Ethanol) 212 nm (E 36,500), 227 sl. sh. (13,350), 252 (12,100), 287 (1,400). C.I. Mass spec. $[m\cdot = H]^+$ for free base at m/z 287.

Exact Mass (Chem. Ionization) Calcd. for $C_{18}H_{27}N_2O$: 287.2123. Found: 287.2123.

Anal. Calcd. for $C_{18}H_{26}N_2O\cdot C_7H_8SO_3$: C, 65.47; H, 7.47; N, 6.11; S, 6.99. Found: C, 65.38; H, 7.61; N, 6.15; S, 6.93.

Example 3 5,6-Dihydro-N,N-dimethyl-4H-benz[de]isoquinolin-5-amine and its Dihydrochloride, Hydrate (4:1):

A. Preparation of cis- and trans-3-(N,N-dimethylamino)-1,2,3,-4-tetrahydro-1-naphthalenecarbonitrile.

A solution of the primary amine (1.68 g, 9.75 mmol) prepared as described in Example 1, part G, 37% aqueous formaldehyde (8 mls), and maleic acid (1.14 g, 9.78 mmol) in methanol (130 mls) was cooled in a water bath (10°C) and sodium cyanoborohydride (6.15 g, 0.0978 mol) was added in one portion. After a few minutes, acetic acid was added to adjust the pH to 6 (litmus). The mixture was stirred for 3 hours, and the solvent was removed in vacuo. The residue was triturated with 30 mls of 15% NaOH and extracted twice with ether. The extracts were extracted three times with 15-20 mls of 10% HCl. The aqueous extracts were washed with ether and basified to pH = 8-9 with conc. NH_4OH. The free base was extracted three times with ether, and the extracts were washed with sat. NaCl and dried ($MgSO_4$). The solvent was removed in vacuo to leave the sub-titled N,N-dimethylamino compound as a light yellow oil (1.59 g, 81%). NMR ($CDCl_3$-TMS) δ2.35 (s,6,N-CH_3), 1.7-3.1 (m, 5), 3.8-4.15 (m,1,CH-CN), 7.0-7.45 (m,4,aromatic H). IR =CH 3064, 3023; C-H 2938, 2893, 2867, 2824; N-C-H 2778; CN 2238; C=C 1604, 1583, 1496; C=C/CH def 1453; C-N/other 1037; γCH 745. UV (Ethanol) End Abs., 207 nm sh. (9,650), 260 sl. sh. (302), 265 (359), 272 (328). Mass spec. m^+ at m/z 200.

Exact Mass Calcd. for $C_{13}H_{16}N_2$: 200.1313. Found: 200.1305.

B. Preparation of 3-(N,N-dimethylamino) 1,2,3,4-tetrahydro-1-naphthalenemethylamine.

Sulfuric acid (100%, 2.95 g, 0.030 mol) was added dropwise to a stirring suspension of lithium aluminum hydride (2.27 g, 0.0595 mol) in THF (100 mls) at 0°C. A solution of the nitrile from part A hereinabove (1.49 g, 7.44 mmol) in THF (50 mls) was added over a three minute period at 0°C and stirred at that temperature for 40 minutes and at room temperature for 1 hour. The mixture was cooled in ice and water (2.3 mls), 15% NaOH (2.3 mls), and water (6.9 mls) were added in succession. The reaction mixture was stirred at room temperature for 1.5 hours and filtered. The aluminum salts were washed with ether, and the combined filtrate was dried ($MgSO_4$). The solvent was removed in vacuo to leave the sub-titled amine as a yellow oil (1.63 g, 100%). NMR ($CDCl_3$-TMS) δ1.5-2.35 (m,5); 2.36, 2.37 (d of s,6,N-CH_3); 2.6-3.2 (m,5); 7.1-7.3 (m,4,aromatic H). IR NH 3363, 3289; =CH 3060, 3018; C-H 2932, 2865, 2824; N-C-H 2777; C=C/NH def 1649, 1602, 1581; C=C/CH def 1491, 1451; CH def 1380; C-N 1036; γCH/-other 767, 744. UV (Ethanol) End abs., 262 nm sh. (E 388), 266 (484), 273 (474), 278 sh. (84). Mass spec. m^+ at m/z 204.

Exact Mass Calcd. for $C_{13}H_{20}N_2$: 204.1626. Found: 204.1619.

C. Preparation of 3-(N,N-dimethylamino)-1,2,3,4-tetrahydro-1-naphthaleneformamide.

A mixture of formic acid (0.57 g, 0.0119 mol) and acetic anhydride (1.14 g, 0.0112 mol) was stirred at room temperature for 50 minutes and cooled in ice. A solution of the primary amine (1.63 g, 7.98 mmol) from part B hereinabove in THF (15 mls) was added over a period of 5 minutes, and the mixture was stirred at room temperature overnight. The solution was diluted with ether and washed twice with 5% NaOH. The washings were back extracted with ether, and the combined organics were washed with Sat. NaCl and dried ($MgSO_4$). The solvent was removed in vacuo to leave the sub-titled amide as a yellow oil (1.45 g, 78%). NMR δ1.7- 2.2 (m,2), 2.34 (s,6,N-CH_3), 2.55-4.05 (m,6), 5.7-6.25 (br.,1,NH), 7.05-7.3 (m,4,aromatic H), 7.9-8.26 (m,1,CHO). IR NH 3275; =CH/NH 3100, 3059, 3020; C-H 2934, 2865; N-C-H 2776; C=O 1666; C=C 1603, 1541, 1492; Amide II 1541; CH

def/C=C/other 1451, 1384; C-N/other 1245, 1037; γCH/other 745. UV (Ethanol) 212 nm sl. sh. (E 11,150), 260 s.. (407), 266 (534), 273 (548). Mass spec. m^+ at m/z 232.

Exact Mass Calcd. for $C_{14}H_{20}N_2O$: 232.1576. Found: 232.1576.

D. Preparation of 3,3a,5,6-Tetrahydro-N,N-dimethyl-4H-Benz-[de]isoquinolin-5-amine:

The amide (1.25 g, 5.38 mmol) from part C hereinabove and polyphosphoric acid (22.5 g) were stirred in an oil bath maintained 160-165°C for 2.5 hours to effect cyclization. The thick mixture was dissolved in water (100 mls) and filtered. The filtrate was cooled in ice and basified with 15% NaOH. The milky mixture was extracted three times with ether, and the combined extracts were washed with sat. NaCl and dried ($MgSO_4$). The solvent was removed in vacuo to leave the sub-titled tri-cyclic amine as a dark brown oil (0.95 g, 82.4%). NMR ($CDCl_3$-TMS) δ1.15-1.7 (m,3); 2.30, 2.38 (d of s,6,NCH_3); 1.95-3.3 (m,5); 3.9-4.15 (m,1); 7.0-7.3 (m,3,aromatic H); 8.25-8.37 (m,1,N=CH). IR 3391; =CH 3064, 3033; CH 2933, 2860, 2816; N-C-H 2770; C=N 1626; C=C 1584; C=C/CH def. 1469, 1452; C-N/other 1235, 1040, 1016; γCH/other 776, 755, 739. UV (Ethanol) 213 nm (E 22,000), 252 sh. (8,150), 258 (9,000), 267 sh. (7,050), 300 sh. (1,250). Mass spec. m^+ at m/z 214.

Exact Mass Calcd. for $C_{14}H_{18}N_2$: 214.1470. Found: 214.1463.

E. Preparation of 5,6-Dihydro-N,N-dimethyl-4H-benz[de]isoquinolin-5-amine and its Dihydrochloride, Hydrate (4:1):

A mixture of the cyclized compound from part D hereinabove (0.88 g, 4.11 mmol) and 10% palladium on carbon (0.20 g) in decalin (16 mls) was stirred at reflux for 2.5 hours. Palladium on carbon catalyst (10%, 0.20 g) was again added, and the reflux was continued for a total of 5 hours. The mixture was filtered through a filter aid (Celite™), and the catalyst was washed well with methylene chloride. The solution was concentrated in vacuo to leave a decalin solution of the titled amine product. The mixture was diluted with ether and extracted 3 times with 10 mls of 10% HCl. The extracts were washed with ether and basified with 40% NaOH while cooling in ice. The free base was extracted three times with ether, and the combined extracts were washed with sat NaCl and dried ($MgSO_4$). The solvent was removed

in vacuo to leave a dark green-black oil (0.47 g). Purification by gravity chromatography (SiO_2; 5% MeOH, 0.5% NH_3, $CHCl_3$) gave a brown oil. The compound was dissolved in ether and filtered, and excess ethereal HCl was added to the filtrate. The solvent was decanted from the precipitate, and the titled salt was washed with ether. Crystallization from methanol/ether gave a tan solid (0.16 g; mp 255-257°C dec.). NMR (DMSO-d^6,TMS) δ2.89 (s,6, NCH3); 3.2-4.0 (m,5,N-CH(CH_2)$_2$); 4.3-5.6 (br., NH^+); 7.8-8.13 (m,2,C-7 and C-8 aromatic H); 8.34, 8.38, 8.43, 8.46 (dd,J=2.8 Hz and 6.7 Hz,1,C-9 aromatic H); 8.60 (s,1,C-3 aromatic H); 9.74 (s, 1,C-1 aromatic H). IR OH/NH 3471, 3409; -CH 3070, 3016; NH^+ 2576, 2450, 2076; C=C/C=N 1641, 1607, 1554, 1493; γCH/other 858, 802, 782, 776. UV (Ethanol) 222 nm (E 53,250), 267 sh. (4,050), 276 (4,900), 288 (4,500), 313 (3,250), 323 sh (3,300), 327 (4,400). Mass spec. m^+ for free base at m/z 212.

Exact Mass Calcd. for $C_{14}H_{16}N_2$: 212.1313. Found: 212.1308.

Anal. Calcd. for $C_{14}H_{16}N_2 \cdot HCl \cdot 1/4\ H_2O$: C, 58.04; H, 6.44; N, 9.67; Cl, 24.47. Found: C, 58.18; H, 6.45; N, 9.65; Cl, 24.17.

Example 4 2,3,7,8,9,9a-hexahydro-N,N,1-trimethyl-1H-benzo[de]-quinolin-8-amine, and its hydrochloride, hydrate (3S) (8R-trans).

A. Preparation of the 3-carbamoyl-α-tetralone amide using isobutyl chloroformate.

A solution of the 1,2,3,4-tetrahydro-4-oxo-2-naphthenoic ketoacid (45.6 g, 0.24 mole) described in Example 1, part C, in 1200 mL of THF was cooled to 5°, triethylamine (29.0 g, 0.288 mole) was added, followed by a solution of isobutyl chloroformate (42.6 g, 0.312 mole) in 500 mL of THF during 30 min keeping the temperature at 5°. The mixture was stirred at 5° for 2 h. Ammonium hydroxide (300 mL) was added over 30 min at 5°, the mixture was stirred for 1 h at this temperature, then for 2 h at room temperature. The mixture was concentrated at 40° in vacuo and 200 mL of H_2O was added. The resulting solid was filtered, washed with H_2O (2 x100 mL) and dried in vacuo at 50° (32.58 g). Crystallization from acetonitrile gave the sub-titled ketoamide in two crops: 27 g melting at 182-182° and 3.41 g melting at 181-182°. Yield - 67%.

B. Reaction of the ketoamide with 2,2-dimethoxyethylamine to form the 3-carbamoyl-1-[2-(dimethoxy)ethylimino]tetralone.

2,2-Dimethoxyethylamine (2.48 g, 0.0236 mole) and triethylamine (12.1 g, 0.12 mole) were added to a solution of the ketoamide from part A hereinabove (3.78 g, 0.02 mole), and it was cooled to 10°. $TiCl_4$ (1.89 g, 0.01 mole) was added dropwise over 5 min at 10° and the mixture was stirred at 10° for 30 min and at R.T. for 18 h. The suspension was filtered through a filter aid (Celite™), and the filtrate was evaporated.

NMR ($CDCl_3$, 500 MHz) was run on sample prepared by the above procedure but where the only amine source was 2,2-dimethoxyethylamine, and showed a ratio of Z:E isomer of 1.76:1 based on the integration of the doublets at δ 8.16 (J = 7.6 Hz) and δ 8.0 (J = 7.6 Hz).

C. Reduction of the imine with $NaBH_4$ to form the cis- and trans-[(2,2-dimethoxyethyl)amino]-1,2,3,4-tetrahydro-2-naphthalenecarboxamide.

The above crude imine from part B hereinabove (5 g) was dissolved in 100 mL of abs. EtOH. $NaBH_4$ (5 g) was added portionwise during 5 min keeping the temperature at 25°. The mixture was stirred at R.T. for 19 h and then evaporated at 40°. $CHCl_3$ and 30 mL of ice cold 1N NaOH were added, and the $CHCl_3$ layer was washed with sat. NaCl solution, dried ($MgSO_4$) and evaporated. The resulting oil (4.57 g) was dissolved in ether and extracted with 5% HOAc (30 mL, 10 mL). The acidic extract was backwashed once with ether, cooled and basified with cold 15% NaOH. Extraction with $CHCl_3$ was done as above to give 4.1 g of an oil. Trituration with ether gave 2.82 g of crystals, mp 86-88°, raised to 89-91° on recrystallization (cis isomer).

The filtrate was evaporated and the residue subjected to MPLC on silica gel using 10% MeOH-$CHCl_3$. (10 mL fractions were collected.) Fractions 10-12 gave an impurity. Fractions 13-16 gave 0.352 g which was crystallized from ether; 0.135 g of the trans-isomer, mp 87-88°.

Fractions 17-19 gave no material. Fractions 20-36 gave 0.460 g of the cis-isomer, mp 88-89°.

Yield of the cis-isomer 3.28 g (59%), trans-isomer: 0.135 g (2.4%).

Cis isomer - uv sh 210 (5,200), sh 254 (228), sh 260 (306), λmax 266 (370), 274 (334). IR NH 3460, 3318, 3196. =CH 3065, 3052. C=O 1669, 1648. NH dec/C=C 1614, 1606, 1577, 1485. C-O/aromatic 1128, 1077, 1056, 783, 759, 747. Mass spec. H.R. Found 278.1615. Calcd. for $C_{15}H_{22}N_2O_3$ 278.1630. NMR ($CDCl_3$ C-H_{ax}-N) as triplet at δ 3.97 (J = 9 Hz).

Anal. Calcd. $C_{15}H_{22}N_2O_3$ for : C, 64.32; H, 7.97; N, 10.07. Found: C, 64.53; H, 7.86; N, 9.37.

Trans isomer: uv sh 254 (234), sh 258 (295), λmax 265 (351), 273 (281), IR NH 3399, 3303, 3203. =CH 3102, 3068. Impurity 2487, 2418. C=O 1653. NH dec./C=C 1621, 1580, 1490. C-)/other 1194, 1141, 1130, 1091, 1099, 1057, 976, 760. Mass spec. HR. Found 278.1619. Calcd. for $C_{15}H_{22}N_2O_3$ 278.1630. NMR ($CDCl_3$) C-H_{eq}.-N as triplet at δ 3.84 (J = 4 Hz).

Anal. Calcd: for $C_{15}H_{22}N_2O_3$: C, 64.72; H, 7.97. N, 10.07. Found: C, 64.80; H, 7.77; N, 10.02.

D. Cyclication of the cis-amide to form 2,3,7,8,9,9a-hexahydro-1H-benzo[de]quinoline-8-carboxamide, and its hydrochloride.

A solid (0.5 g; 1.8 mmole) portion of the cis-isomer-carboxamide from part C hereinabove was added portionwise over 10 min with stirring to 3 mL of 76.5% H_2SO_4 keeping the temperature at 0°, and the mixture was stirred at 0° for 1 h. TLC (silica gel, 10% MeOH-$CHCl_3$, 1% NH_4OH) showed the disappearance of starting material. [A small aliquot was worked up with cold NaOH and NMR ($CDCl_3$-CD_3OD) showed a multiplet at δ 3.6 corresponding to CH-O in support of the structure of the intermediate shown in the Chart D, step D, (1)].

The above solution was transferred to an ice-cooled hydrogenation bottle using 6 mL of ice-cold H_2O; 180 mg of 5% Pd-C was added and the mixture was hydrogenated at initial pressure of 51.6 p.s.i. for 21 h. It was filtered, cooled to 0° basified with cold 20% NaOH, saturated with NaCl, and extracted with $CHCl_3$. The extract was washed with sat. NaCl solution, dried ($MgSO_4$) and evaporated to give 0.2 g (51% yield) of the sub-titled carboxamide as a colorless gum, which was suitable for the next step. NMR was compatible with the sub-titled compound. [Step D, (2)].

The hydrochloride was formed in MeOH with etheral HCl, mp 308°

dec. IR C=O 1692. Mass spec. FAB: Found 217.1337. Calcd. for $C_{13}H_{17}N_2O$ 217.1341.

Anal. Calcd. for $C_{13}H_{16}N_2O \cdot HCl$: C, 61.77; H, 6.78; Cl, 14.03; N, 11.09. Found: C, 61.33; H, 6.67; Cl, 13.67; N, 10.72.

E. Preparation of trans-ethyl 8-(aminocarbonyl)-2,3,7,8,9,9a-hexahydro-1H-benzo[de]quinoline-1-carboxylate ester.

Et_3N (80 mg, 0.8 mmole) was added to a solution of the carboxamide from part D hereinabove (0.11 g, 0.5 mmole) in 10 mL of THF, followed by dropwise addition of a solution of ethyl chloroformate (60 mg, 0.55 mmole) in 1 mL of THF. The mixture was stirred 1 h and evaporated. The residue was taken up in $CHCl_3$-H_2O and the $CHCl_3$ was washed with sat. NaCl solution, dried ($MgSO_4$) and evaporated. The residue (0.138 g) was subjected to MPLC using 1% MeOH, $CHCl_3$ (3 mL fractions were collected). Fractions 1-19 gave a trace of an impurity. Fractions 20-30 and 31-36 (10% MeOH-$CHCl_3$) gave 0.11 g (77% yield) of pure sub-titled ester (U-72579). The analytical sample was prepared from ether, mp 164-165°. IR NH 3387, 3318, 3182. =CH 3025, 3030. C=O 1691, 1666. NH def/C=C 1639, 1595, 1539, 1484; C-O/C-N/-other 1309, 1378, 1219, 1200, 1120, 1021, 767. Mass spec. FAB. Found 289.1557. Calcd. for $C_{16}H_{21}N_2O_3$ 289.1552. NMR ($CDCl_3$) 200 MHz confirmed the structure.

Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.64; H, 6.99; N, 9.72. Found: C, 66.20; H, 7.07; N, 9.42,

F. Preparation of 8-amino-2,3,7,8,9,9a-hexahydro-1H-benzo[de]-quinoline-1-carboxylate ester, and its (2)-2-butenedioate (1:1) salt.

Bis(trifluoroacetoxy)iodobenzene (1.24 g; 2.88 mmole) was added portionwise during 1 min to a solution of the aminocarbonyl-carboxylate ester from part E (0.56 g; 1.92 mmole) in 9 mL of THF and 6 mL of H_2O. The resulting solution was stirred at R.T. for 21 h. It was then cooled, 9 mL of ice-water was added, followed by 3mL of 10% HCl and extracted with ether. The aqueous solution was cooled, basified with 15% NaOH, saturated with NaCl, and extracted with $CHCl_3$ (4 x 15 mL). The extract was washed with saturated NaCl solution, dried ($MgSO_4$) and evaporated at 40°; 420 mg. (84% yield) of the sub-titled ester as an oil. The maleic acid salt was formed in ether and was crystallized from MeOH-ether; mp 185-186° dec. UV sh 217 (22,600).

IR NH+/acid OH 3043, 2738, 2664, 2529; =CH 3225; C=O 1689; C=C/NH_3^+ 1642, 1634, 1610, 1596, 1518, 1484; CO_2^- 1563, C-O/C-N/other 1209, 1108, 1046, 870, 766. Mass spec. FAB : Found: 261.1597. Calcd. for $C_{15}H_{21}N_2O_2$ 261.1603. NMR (D_2O) 200 MHz was compatible with the desired compound.

Anal. Calcd. for $C_{15}H_{20}N_2O_2 \cdot C_4H_4O_4$: C, 60.62; H, 6.43; N, 7.44. Found: C, 60.37; H, 6.52; N, 7.35.

G. Preparation of trans-ethyl 8-(dimethylamino)-2,3,7,8,9,9a-hexahydro-1H-benzo[de]quinoline-1-carboxylate ester and its (2)-2-butenedioate (1:1) salt.

A solution of the 8-primary amine compound from part F hereinabove (1.98 g, 7.6 mmole) in abs. EtOH (48 mL), 37% formalin (6.67 mL, 0.086 mole), HOAc (0.46 mL, 7.6 mmole) and 340 mg of 10% Pd-C was hydrogenated for 19 h at initial pressure of 49.5 p.s.i. The mixture was filtered, evaporated, the residue was taken up in $CHCl_3$ and cold 15% NaOH. The $CHCl_3$ extract was washed with sat. NaCl solution, dried ($MgSO_4$) and evaporated to form the sub-titled 8-N,N-dimethylamine. The sub-titled maleic acid salt (U-72806E) was formed in ether, and was crystallized from MeOH-ether, mp 145-146°. UV sh 213 (27,250), IR = CH 3022, NH^+/acid OH 2630, 2336; C=O 1693. C=C/CO2-/-other 1620, 1582, 1523, 1464, 1427, 1355. C-O/C-N/other 1203, 1110. 1059, 868, 768, 760. Mass spec. FAB $[M\cdot + H]^+$ 289. NMR ($CDCl_3$) was compatible.

Anal. Calcd. for $C_{17}H_{24}N_2O_2 \cdot C_4H_4O_4 \cdot 1/4\ H_2O$: C, 61.67; H, 7.02; N, 6.85. Found: C, 61.38; H, 7.30; N, 6.77.

H. Preparation of 2,3,7,8,9,9a-hexahydro-N,N,1-trimethyl-1H-benzo[de]quinolin-8-amine, and its hydrochloride hydrate (3S) (8R, trans).

A solution of the N,N-dimethylamine from part G hereinabove (1.7 g; 5.9 mmole) in 15 mL of THF was added to a solution of LAH (1.7 g) in 40 mL of THF, keeping the T at 25°. The mixture was stirred for 20 h. It was treated in succession with 1.7 mL H_2O, 1.7 mL 15% NaOH, 5.1 mL of H_2O and stirred for 1 h. It was filtered and evaporated, the residue was subjected to MPLC on silica gel using 5% MeOH-$CHCl_3$. (10 mL fractions were collected). Fractions 24-27 contained an impurity. Fractions 28-32 contained the same impurity and the desired

product.. Fractions 33-38 (10% MeOH-$CHCl_3$) gave the pure end product amine compound product. The dihydrochloride was formed in ether, and was crystallized from MeOH-ether, mp 311° dec. IR OH 3380;=CH 3029 NH^+ 2574, 2473; H_2O 1628; C=C 1597; C-N/other 1002, 952, 793. Mass spec. FAB: Found 231.1863. Calcd. for $C_{15}H_{23}N_2$ 231.1861. NMR (D_2O) was compatible with the desired compound.

Anal. Calcd. for $C_{15}H_{22}N_2 \cdot 2$ HCl.3/4 H_2O: C, 56.87; H, 8.11; Cl, 22.39; N, 8.84. Found: C, 56.89; H, 7.79; Cl, 22.67; N, 8.73.

Example 5 7,8,9,9a-Tetrahydro-8-amino-1H-benzo[de]quinolin.

A. Preparation of 8,9-Dihydro-7H-Benzo[de]quinoline-8-carboxamide.

Cis-4-[(2,2-dimethoxyethyl)amino]-1,2,3,4-tetrahydro-2-naphthalenecarboxamide from Example 4 part C (5 g; 0.018 mole) was added portionwise during 10 min to conc. H_2SO_4 (30 mL) at 0°, and stirred for 1 h at 0°. The solution was then stirred for 2 h at R.T. Palladium on carbon catalyst (0.5 g) was added and air was bubbled through the suspension for 20 h. The mixture was poured onto 100 mL of ice-water. The catalyst was filtered and washed with H_2O. The filtrate was basified with ice-cold 20% NaOH keeping the temperature at 5° with an ice bath. The mixture was then stirred at R.T. for 1 h, the solid was collected by filtration, washed with H_2O and dried at 50°; brown solid, 3.4 g. The filtrate was extracted with $CHCl_3$. The extract was washed with sat. NaCl solution, dried ($MgSO_4$) and evaporated to give an additional 0.14 g. of the desired sub-titled product. The above two crops were combined and crystallized from MeOH-$CHCl_3$; 1.35 g, mp 238° dec/ The filtrate was evaporated and the residue subjected to MPLC on silica gel using 3% MeOH-$CHCl_3$ (20 mL fractions were collected). Fractions 24-44 gave 0.83 g of additional sub-titled compound, mp 237° dec. Yield: 2.18 g (57%).

UV λmax 222 (46,400), sh 268 (3,550), 276 (4,350), 288 (4,000), sh 304 (5,150), 314 (3,600), sh 324 (3,800), 328 (4,400). IR NH 3370, 3174; =CH 3053; amine salt 2533, 2475, 2398, 2360; C=O 1669. NH def/C=C 1619, 1591, 1577, 1518, 1498. C-N/other 1351, 1341, 1321, 834. Mass spec. FAB - Found 213.1041. Calcd. for $C_{13}H_{13}N_2O$: 213.1028. NMR ($CDCl_3$-CD_3OD) δ 8.29 (d, J = 7Hz, 1H, =CH-N), 7.7-7.4

(m, 4H, aromatic), 3.5-2.75 (m, rest).

Anal. Calcd. for $C_{13}H_{12}N_2O \cdot 1/6\ H_2O$: C, 72.54; H, 5.77; N, 13.02. Found: C, 72.65; H, 5.99; N, 12.88.

When crystalline trans-isomer of the starting-naphthalenecarboxamide was used in the above cyclization the total yield of the purified product was 45%. When the oily mixture of cis- and trans isomers was used, the yield was considerably lower.

B. Preparation of 8,9-Dihydro-7H-Benzo[de]quinoline-8-carboxylic acid.

A mixture of the quinoline-carboxamide from part A hereinabove (3.28 g, 0.015 mole) and 250 mL of 10% NaOH was refluxed for 1 h (a clear solution resulted after 15 min). The solution was cooled, acidified with conc. HCl (ca 70 mL) to pH 7 and freeze-dried. The resulting solid was ground to a fine powder and extracted with warm 25%-isopropanol-$CHCl_3$ (3 x 300 mL). The extract was dried ($MgSO_4$) and evaporated to give 3 g (94% yield) of the sub-titled acid as a tan solid, mp 225-227-dec.

UV λmax 221 (51,000), 257 (2.740), 267 (3,870), (4,750), 288 (4,300), 303 (2,120), 314 (3,920), 323 (4,060), 327 (4.840); IR =CH 3072, 3053. acid OH 2449 - 1960b. C=O 1709, C=N/C=C 1621, 1593, 1581. C-O/other 1307, 1241, 1216, 832, 732. Mass spec. FAB: Found 214.0858. Calcd. for $C_{13}H_{12}NO_2$ 214.0868. NMR ($CDCl_3$-CD_3OD) δ 8.0 (d, J = 8Hz, 1H =CH-N), 7.75-7.35 (m, 4H, aromatic), 3.6-3.0 (m, rest).

Anal. Calcd. for $C_{13}H_{11}NO_2 \cdot 1/3\ H_2O$: C, 71.22; H, 5.36; N, 6.39. Found: C, 71.64; H, 5.22; N, 6.41.

C. Preparation of 8,9-dihydro-7H-Benzo[de]quinoline-8-(methoxycarbonylamine)(methylcarbamate).

A suspension of the finely ground quinoline-8-carboxylic acid from part B hereinabove (0.21 g; 1 mmole) in 25 mL of acetone was refluxed 10 min and cooled to R.T. A solution of Et_3N (0.111 g; 1.1 mmole) in 1 mL of acetone was added and the suspension stirred for 30 min. The suspension was cooled to -5° to -10° and was kept at this temperature until the work-up. A solution of ethyl chloroformate (0.119 g; 1.1 mmole) in 1 mL of acetone was added during 5 min and stirred for 15 min. Then a solution of NaN_3 (0.325 g, 5 mmole) in 2 mL of H_2O was added over 5 min and the mixture was stirred for 2 h.

It was then poured onto 20 mL of ice water, saturated with NaCl, and extracted with ether (4 x 20 mL), the extract was washed twice with saturated NaCl solution and concentrated to a small volume (ca 3 mL). (On another occasion, when all the solvent was removed, decomposition occurred after a few minutes.) Benzene (10 mL) was added and the solution was refluxed for 10 min, it was followed by IR by disappearance of the azide band at 2150 cm^{-1} and presence of the isocyanate band at 2250. The solution was cooled, 10 mL of MeOH was added and refluxed for 25 min. The reaction was followed by IR until the isocyanate band disappeared (on a layer scale this took 45 min). The solution was evaporated to give the sub-titled compound as a brown solid, 0.142 g. (59% yield) suitable for the next step.

The analytical sample was prepared from ether-petroleum ether (30-60°), mp 156-157° dec.

UV λmax 222 (53,800), sh 257 (2,910), 266 (4,060), 276 (5,030), 288 (4,650), sh 303 (2,300), 314 (4,200), 324 (4,370), 328 (5,250). IR NH/=CH 3295, 3058. C=O 1708, 1689, C=C/C=N 1618, 1586, 1576, 1490. amide II 1545. C-O/C-N/other 1238, 1235, 1044, 835, 764. Mass spec. FAB: Found 243.1133. Calcd. for $C_{14}H_{15}N_2O_2$ 243.1133. NMR ($CDCl_3$) δ 8.39 (d, J = 8 Hz, 1H, =CH-N), 7.65-7.25 (m, 4H, aromatic), 4.75 and 4.45 (two m, broad, 2H, -CH-NH-), 3.65 (s, 3H, CH3), 3.5-2.85 (m, rest).

Anal. Calcd. for $C_{14}H_{14}N_2O_2 \cdot 1/6\ H_2O$: C, 68.54; H, 5.88; N, 11.42. Found: C, 68.30; H, 5.72; N, 11.28.

D. Preparation of 7,8,9,9a-tetrahydro-8-amino-1H-benzo[de]-quinoline.

A mixture of the methyl carbamate from part C hereinabove (0.17 g, 0.7 mmole) and 10 mL of 10% NaOH was stirred and refluxed for 1 h. Tlc indicated disappearance of starting material and a slower moving spot (silica gel, 10% MeOH-$CHCl_3$). The mixture was cooled and extracted with $CHCl_3$. The extract was washed with saturated NaCl solution, dried ($MgSO_4$), and evaporated to give 0.104 g (79% yield) of the titled amine as an oil. NMR (in $CDCl_3$) was compatible with the desired compound.

Example 6

This example illustrated the pharmacological data of representa-

tive compounds of this invention in standard laboratory animal dopamine autoreceptor agonist activity tests, based upon the ability of low (0.1 mg/kg or lower) doses of the test compound to antagonize d-amphetamine induced locomotor stimulation in the animal. The test is believed to provide a reasonable accurate prediction of possible CNS anti-psychotic activity of the test compounds in later higher animal and human clinical tests of the selected clinical candidate compound(s).

It has been found that the representative compounds of this invention gave potent activities in this test (effective at doses from 0.1 mg/kg to as low as 0.001 mg/kg, for the more potent compounds). Although positive identification of the pharmacological mechanisms by which these compounds show their encouraging anti-psychotic activity must depend upon further experimental studies, these test results strongly suggest a useful range of anti-psychotic activity for these compounds.

The test method used to obtain the data set forth below can be described as follows.

Antagonism of d-amphetamine stimulation - Pairs of male Carsworth Farm (CF)-1 mice (18 to 22 gm) were randomly assigned to Woodward circular actophotometer cages. After 30 minutes of acclimation, the mice were injected subcutaneously with 1 mg/kg of d-amphetamine and the indicated dosage treatments (e.g., 10 mg, or 1 mg or 0.1 mg/kg of mouse body weight, of the test compound, dissolved or suspended in Vehicle #122 - (a 0.25 percent w/v carboxymethylcellulose in water suspension), and returned to the cages. Starting 10 minutes after injections, the locomotor activities of the mice were recorded for a period of 20 minutes. Nine treatment groups (n = 12, 24 mice/-group), including appropriate controls were run for each dosage rate experiment. The test result data are expressed as the percent change from d-amphetamine control groups. The statistical significance of these changes was determined by comparing the groups test results with Student's t-test with $p < 0.05$ considered indicative of significant change.

The following representative compounds, the various dosages administered to test groups of animals and the percent changes from the

controls that were observed indicate activity of the test compounds as potential anti-psychotic drug compounds.

Test Compound	Dose (mg/kg)	% Change
Apomorphine	0.1	↓ 45
(a known standard)	0.01	↓ 38
	0.001	↓ 8
(-)3-PPP	3	↓ 60
(a known standard)	0.3	↓ 6
(+)3-PPP	3	↓ 78
(a known standard)	0.3	↓ 61
	0.03	↓ 13
U-71494E	0.1	↓ 44
(Example 1, Section P)	0.001	↓ 3
(first described compound)		
U-71495E	0.1	↓ 65
(Example 1, Section P)	0.01	↓ 24
(Second described compound)		
U-72715A	0.1	↓ 29
(Example 2, Section E)	0.01	↓ 12
U-72717E	0.1	↓ 90
(Example 2, Section G)	0.01	↓ 48
(Second band compound)	0.001	↓ 43
	0.0001	↓ 7
U-72806E	0.1	↓ 32
(Example 4, Section G)	0.01	↓ 7
U-72859E	0.1	↓ 33
(Example 4, Section H)	0.01	↓ 30
	0.001	7

U-73076A	0.1	↓ 37
(Example 2, Section F)	0.01	↓ 43
	0.001	↓ 2

Examples 7 & 8 Pharmaceutical Tablet Compositions.

One thousand tablets for oral use, each containing about 70 mg of (I) 5,6-dihydro-N,N-di-n-propyl-4H-benz(de)isoquinolen-5-amine, (E) 2-butenedioate (2:3) salt from Example 1 or (II) (3a,S-trans)-5-(di-n-propylamino) 3a,4,5,6-tetrahydro-1H-benzo(de)quinolin-2(3H)-one, mono(4-methylbenzenesulfonate, from Example 2 as the essential active ingredient are prepared from the following ingredients:

Essential active ingredient	70 gm
Dicalcium phosphate	150 gm
Methylcellulose, USP (15 cps)	6.5 gm
Talc	20 gm
Calcium stearate	2.0 gm

The essential active ingredient and dicalcium phosphate are mixed well, with 7.5% aqueous solution of methylcellulose, passed through a No. 8 screen and dried carefully. The dried granules are passed through a No. 12 screen, mixed with the talc and stearate and compressed into tablets. These tablets are useful in the treatment of psychoses in adult humans at a dose of 1 tablet 1-4 times a day as needed.

Examples 9 & 10 Pharmaceutical Gelatin Capsule Composition, for oral use.

One thousand two-piece hard gelatin capsules for oral use, each capsule containing 70 mg of compound I or II named in Examples 7 & 8, as the essential active ingredient are prepared from the following ingredients:

Essential active ingredient	70 gm
Lactose, USP	100 gm
Starch, USP	10 gm
Talc, USP	5 gm
Calcium stearate	1 gm

The finely powdered materials are mixed thoroughly, then filled

into hard gelatin capsules of appropriate size.

One capsule 4 times daily is useful for the treatment of psychoses in adult humans.

Examples 11 & 12 Pharmaceutical Composition Soft Elastic Capsule formulations.

One-piece soft elastic capsules for oral use, each containing 100 mg of compound I or II, named in Examples 7 & 8 as the essential active ingredient are prepared in the usual manner by first dispersing the active material in sufficient corn oil to render the material capsulatable.

One capsule two times daily is useful in the treatment of psychoses in adult humans.

Example 13

An aqueous oral preparation containing in each teaspoonful containing 50 mg of compound I named in Examples 7 & 8, as its succinate salt as the essential active ingredient is prepared from the following ingredients:

Essential active ingredient	100	gm
Methylparaben, USP	7.5	gm
Propylparaben, USP	2.5	gm
Saccharin	12.5	gm
Glycerine	3000	ml
Tragacanth powder	10	gm
Orange oil flavor	10	gm
Orange II	7.5	gm
Deionized water, q.s. to	10000	ml

The foregoing aqueous preparation is useful in the treatment of psychoses at a dose of 1 teaspoonful 4 times daily.

Example 14

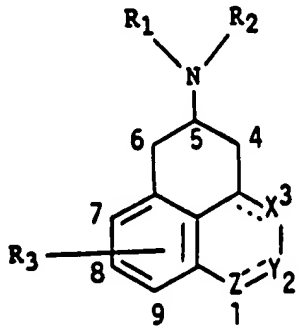
A sterile, aqueous suspension for intramuscular injection and containing in each milliliter 50 mg of the amine compound II, named in Examples 7 & 8, as its succinate salt as the essential active ingredient is prepared from the following ingredients:

Essential active ingredient	5	gm
Polyethylene glycol 4000, USP	3	gm
Sodium chloride	0.9	gm

Polysorbate 80, USP	0.4	gm
Sodium metabisulfite	0.1	gm
Methylparaben, USP	0.18	gm
Propylparaben, USP	0.02	gm
Water for injection, q.s. to	100	ml

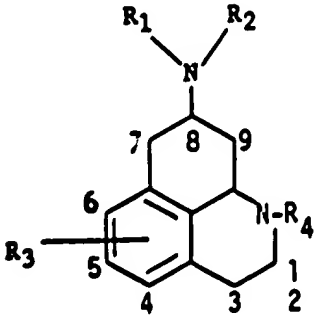
The preceding sterile injectable is useful in the treatment of paranoia psychosis at a dose of one-half to 2 ml.

NOMENCLATURE AND NUMBERING CHARTS

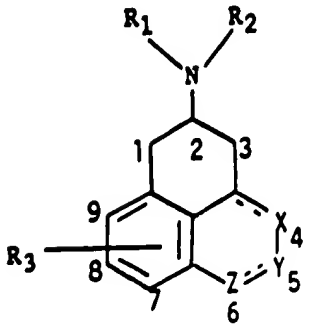


(Chemical Abstracts System)

Benzo-quinolines or
Benzo-isoquinolines
Benzo-quinolin-2-ones

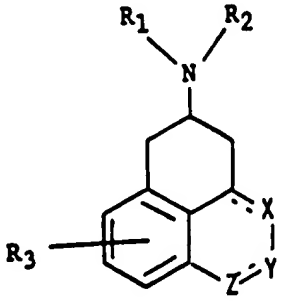


(Chemical Abstracts System)
(Example 4)

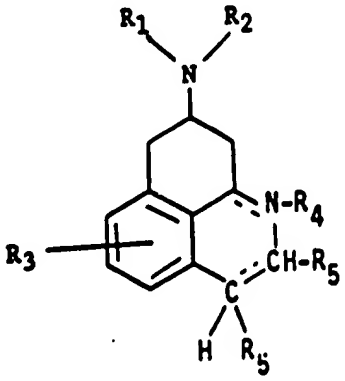


(Applicants system, to show relative positioning)

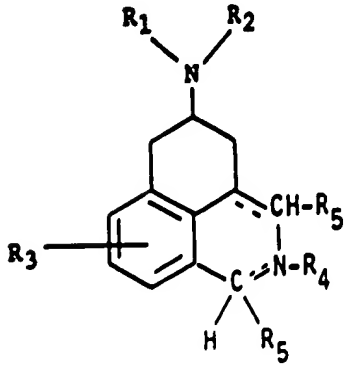
CHEMICAL FORMULAE



(I)

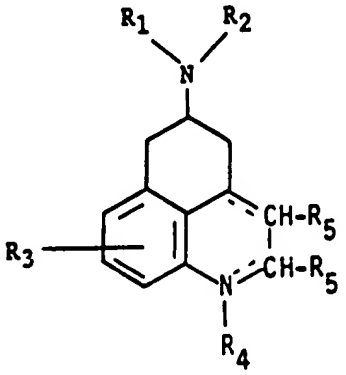


(II)

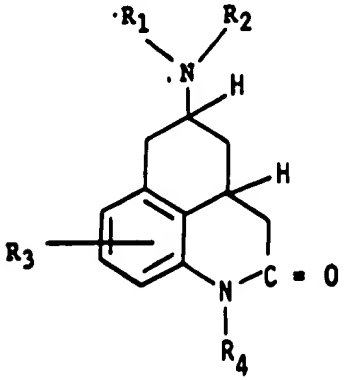


(III)

CHEMICAL FORMULAE (continued)



(IV)



(V)

CHART A

Preparation of Starting Materials

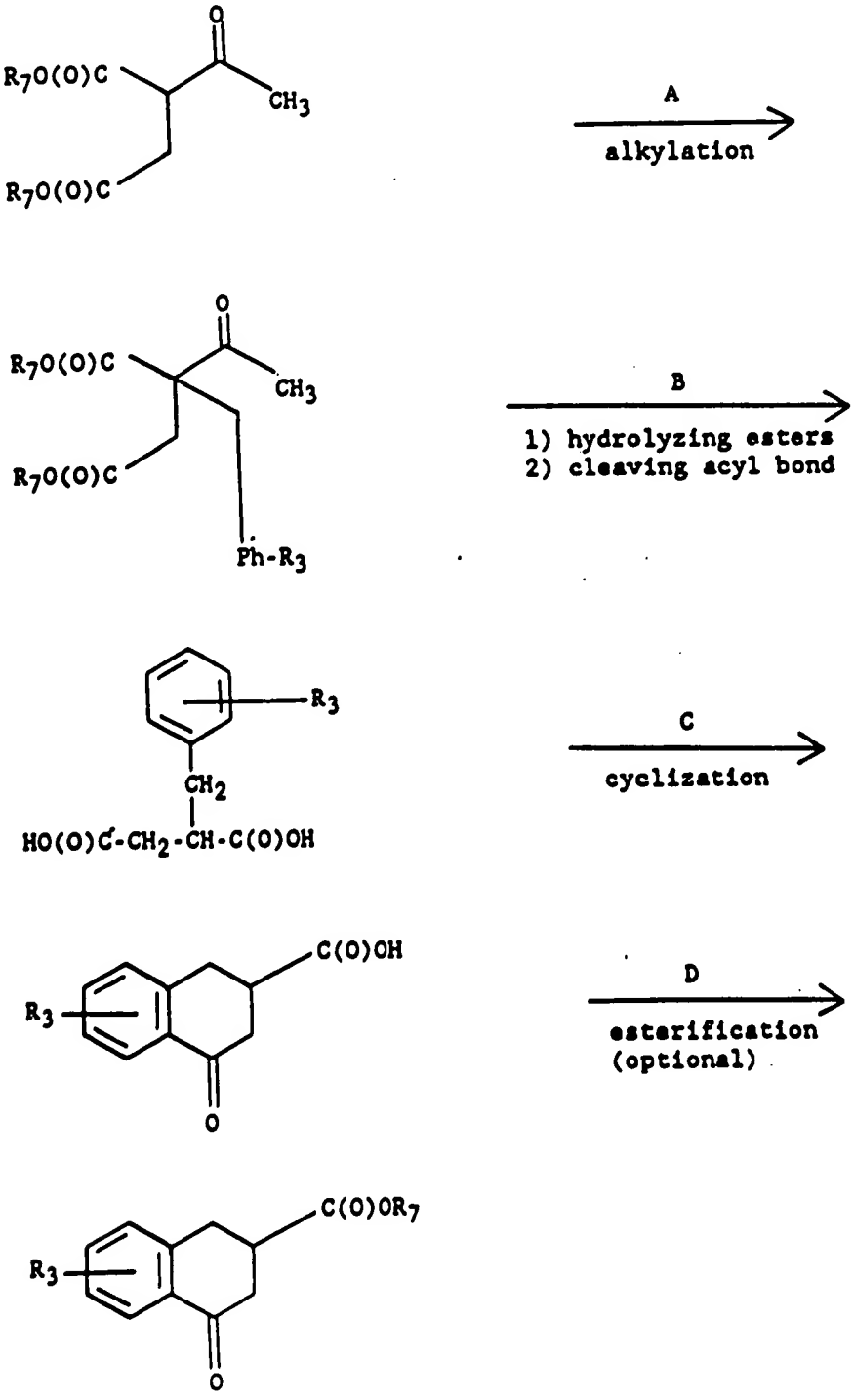
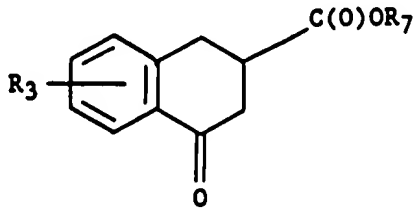


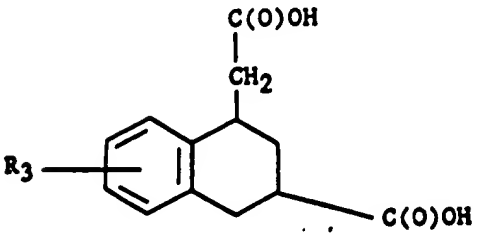
CHART B

Preparation of 5-Amino-Tetrahydro Benzo-Quinolin-2-(3H)-Ones (Aza-Ring Nitrogen in 6-Position relative to 2-Amino nitrogen).



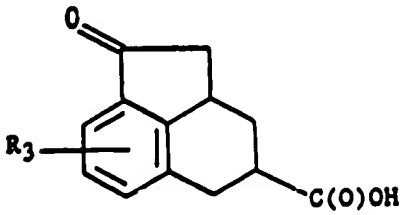
A

1) Reformatsky addition
2) hydrogenolysis
3) hydrolysis



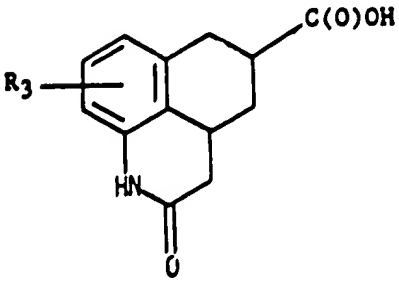
B

1) acid halide formation
2) modified Friedal-Crafts acylation



C

Schmidt Reaction
ring expansion lactam



D

modified Curtis Rearrangement to form the urethane

CHART B (continued)

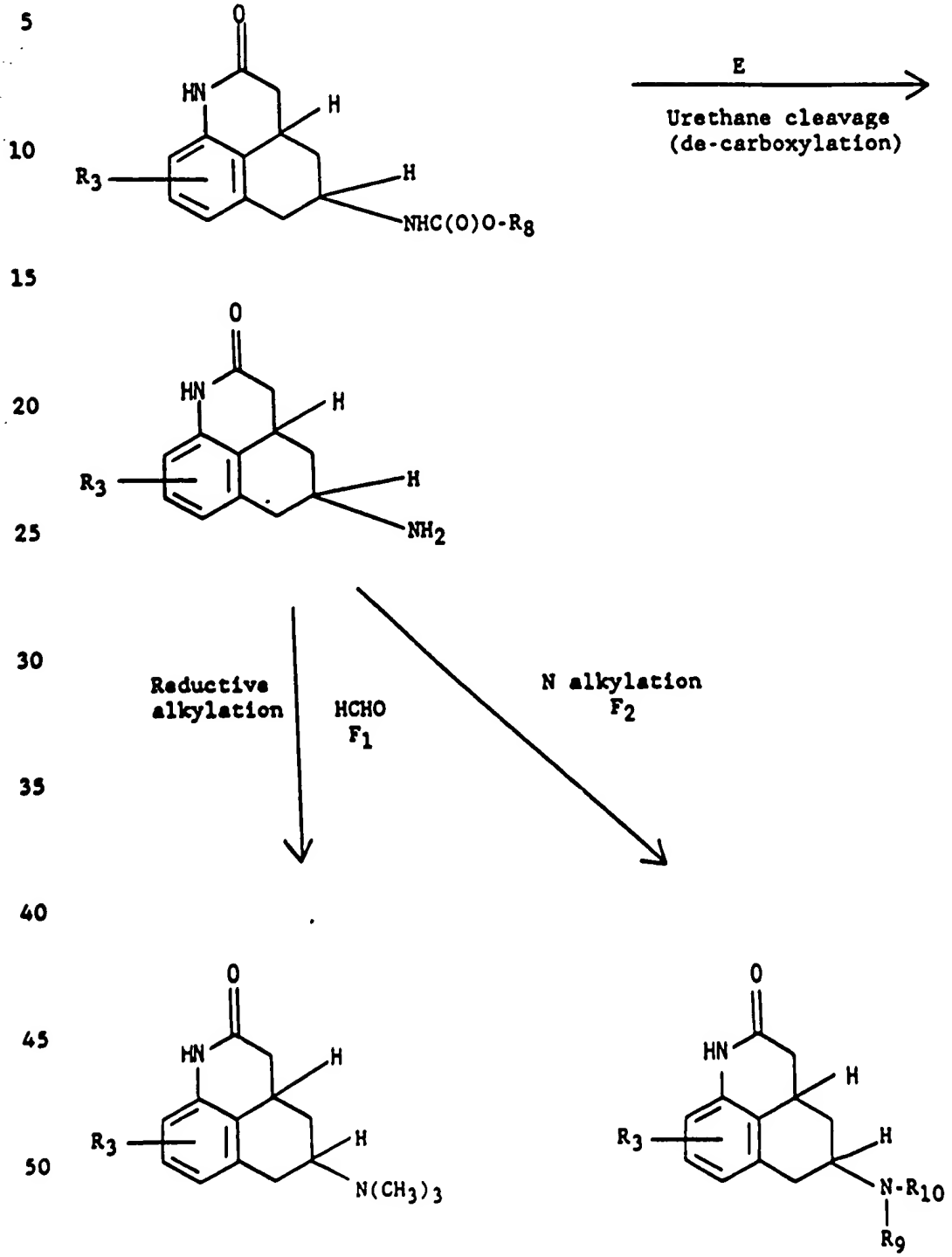
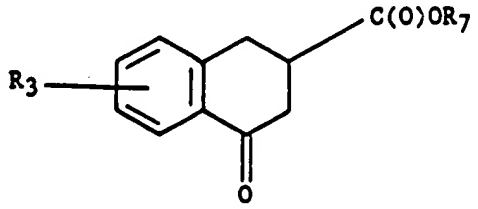


CHART C

Preparation of 5,6-Dihydro-N,N-Dialkyl-4H-Benz[de]isoquinolin-5-Amine and salts thereof.

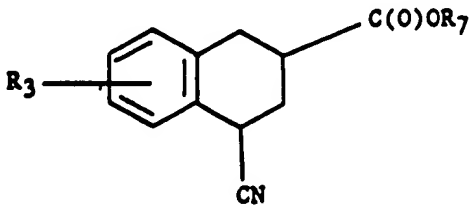
(Aza-ring nitrogen in 5-position relative to the 2-Amino nitrogen)



A

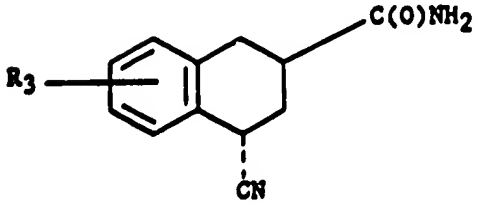
1) cyanohydrin formation
2) hydrogenolysis (reductive cyanation of the ketone)

(from Chart A)

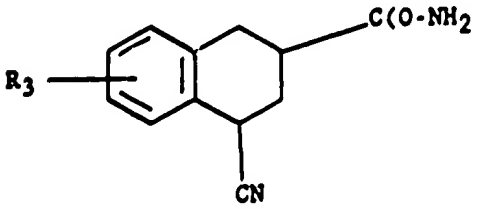


B

amidation



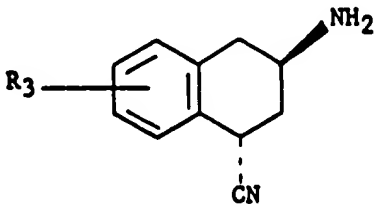
\+ (either or mixed isomers)



C

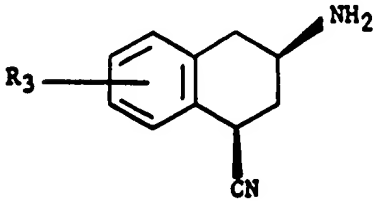
Hofmann
(no bromine)
(amine formation)

CHART C (continued

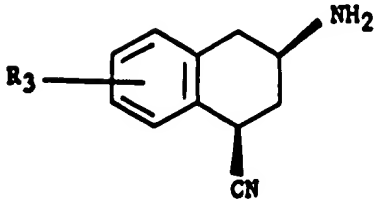


•HCl

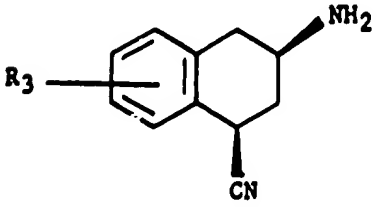
+



or



mixed isomers



•salt

CHART C (continued)

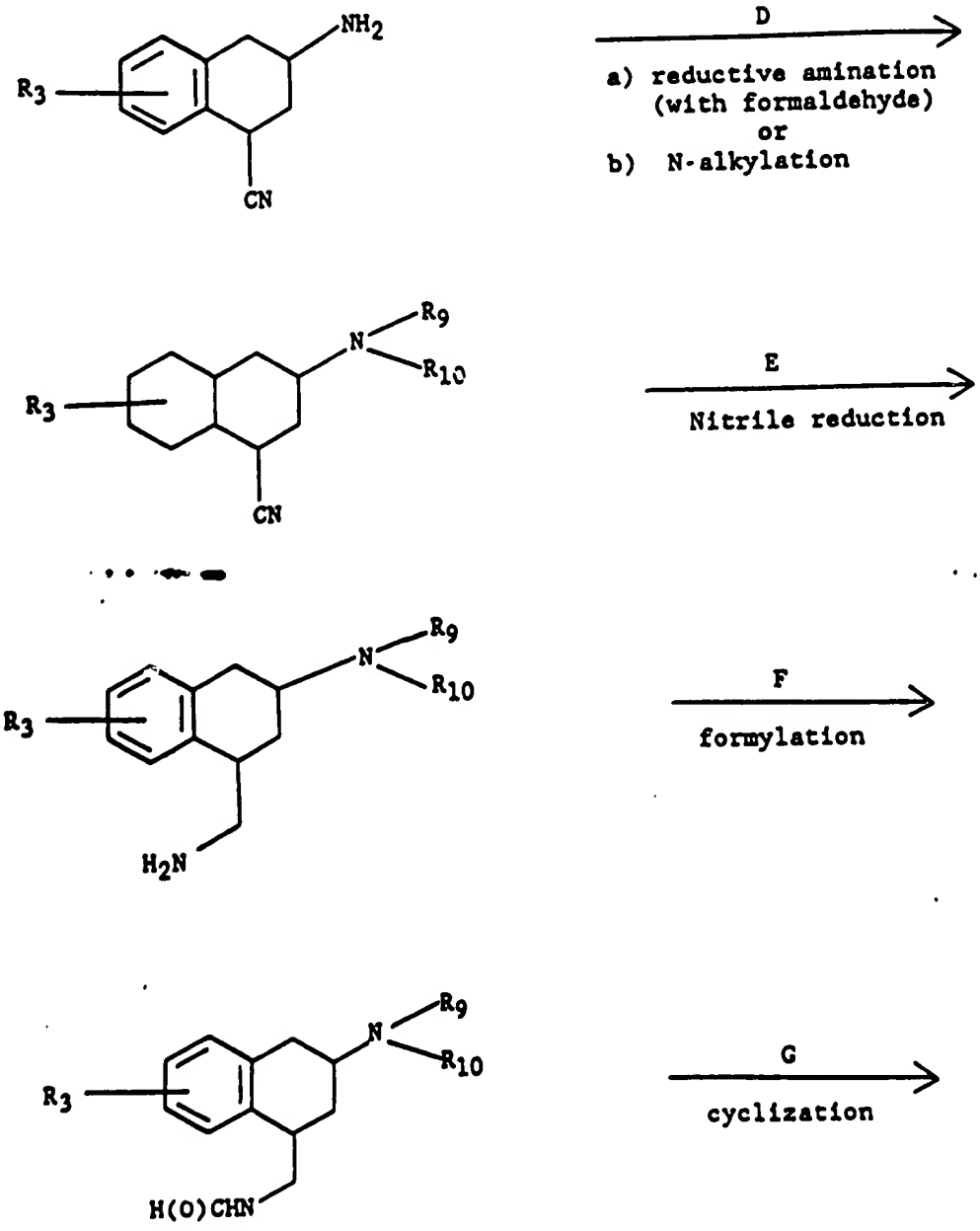


CHART C (continued)

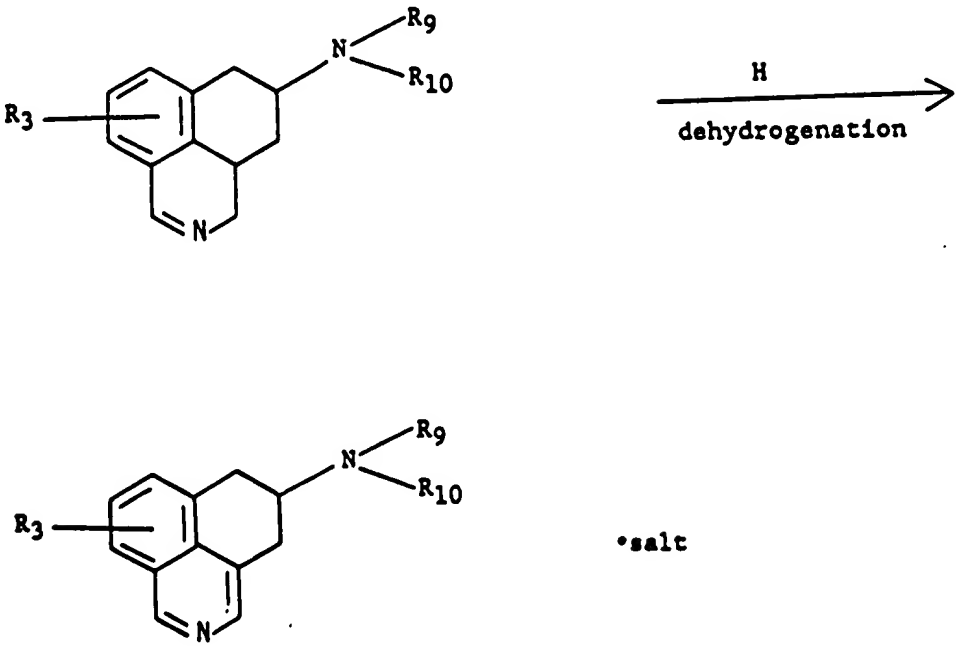


CHART D

Preparation of Hexahydro-N,N,1-Tri-Substituted 1H-Benzo[de]quinolin-8-amines, and salts thereof.

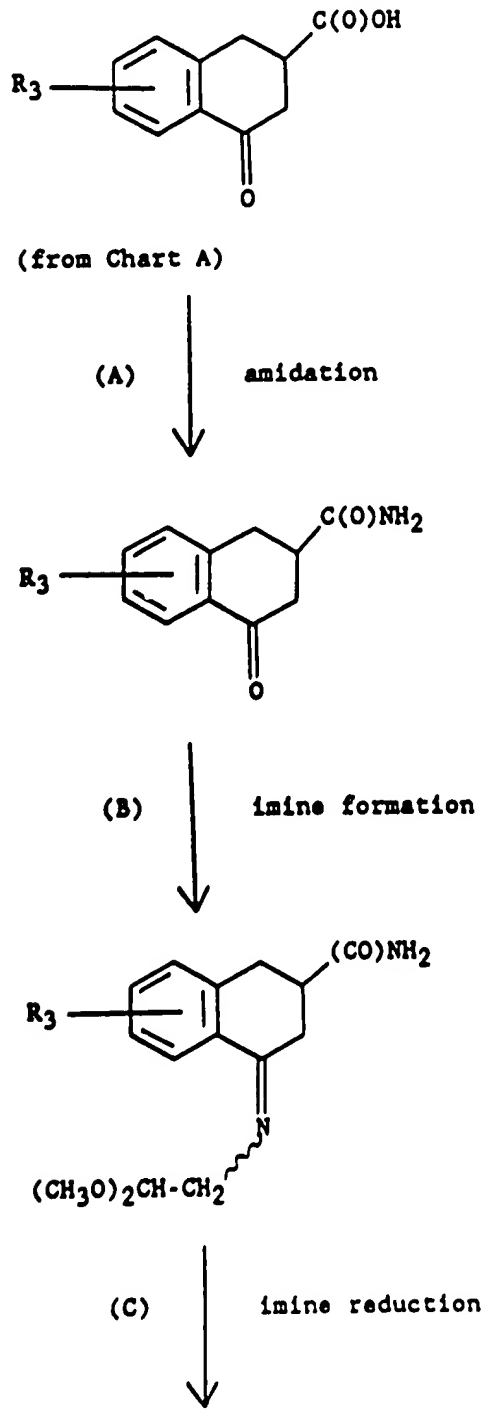


CHART D (continued)

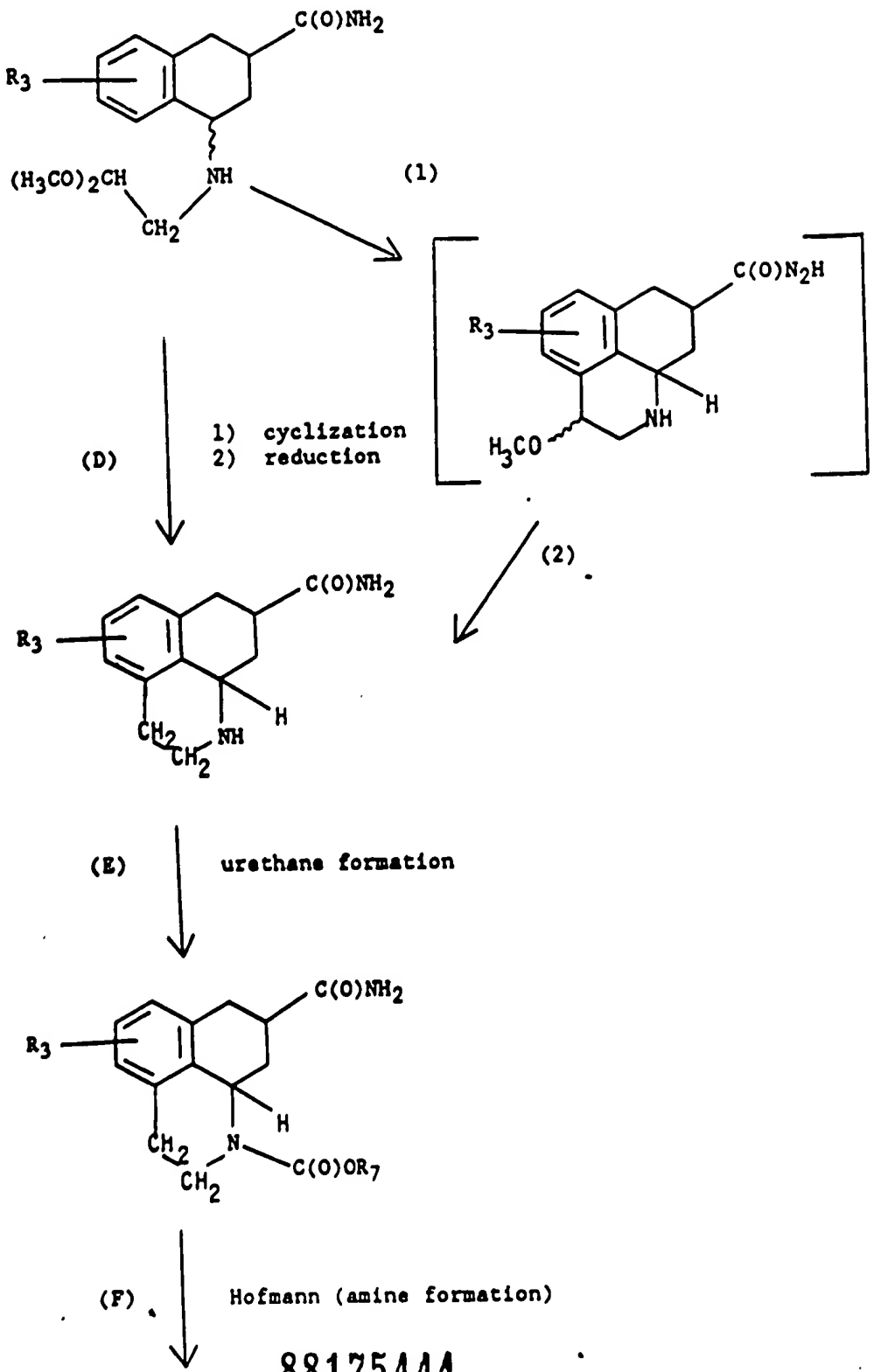
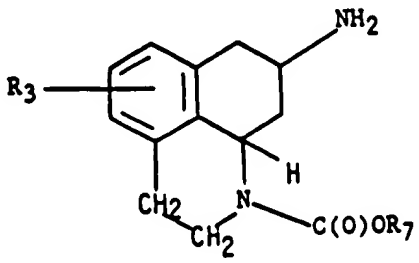
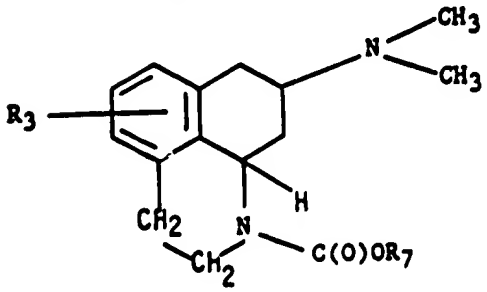


CHART D (continued)



(G) reductive alkylation (formaldehyde) or N-alkylation



(H) Reduction of urethane

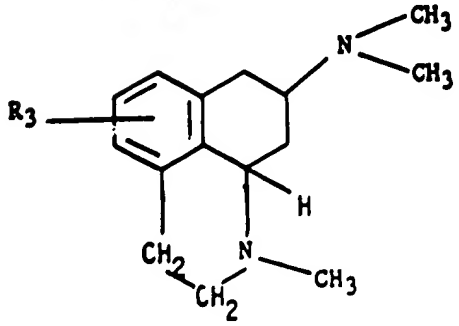
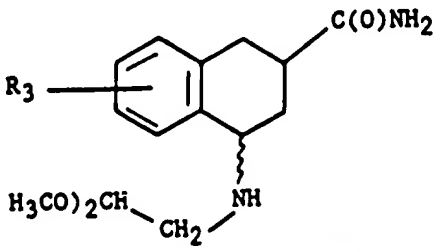


CHART E

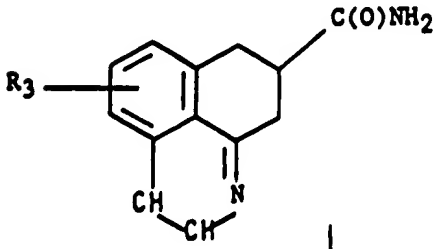
Preparation of a Tetrahydro-8-Amino-1H-Benzo[de]quinoline

(AZA ring nitrogen is in the 4-position relative to the 2-Amino nitrogen position)

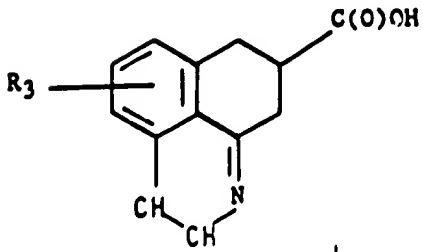


(from Chart D)

(A) 1) cyclization 2) dehydrogenation

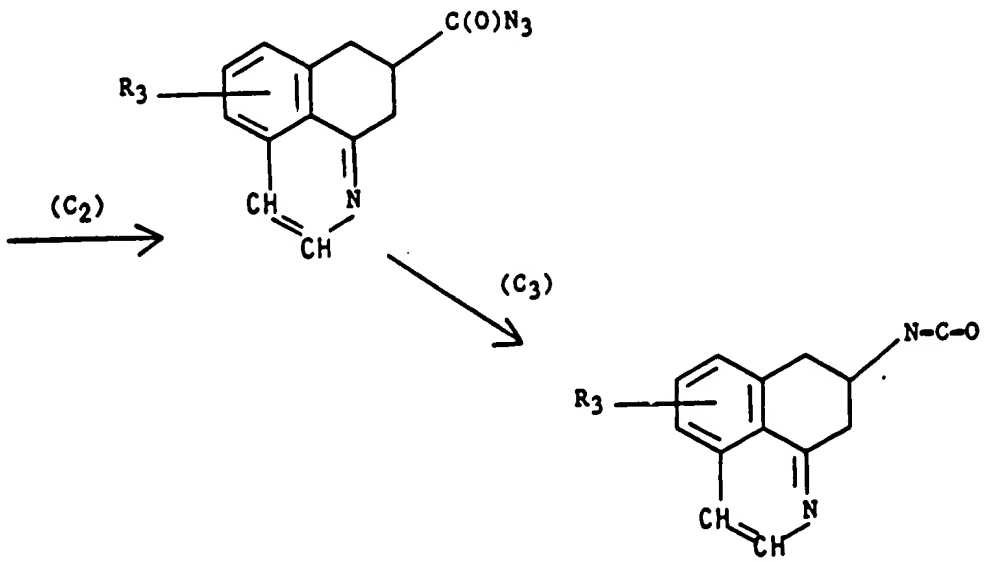


(B) hydrolysis

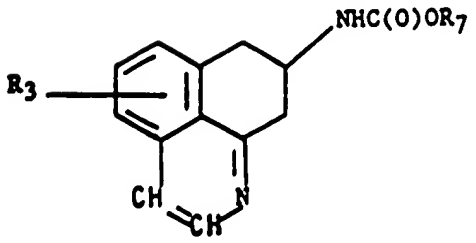


(C) Curtis Reaction
(C_1)

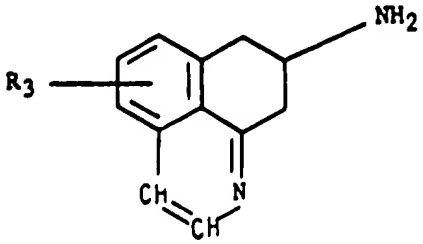
CHART E (continued)



to form the urethane

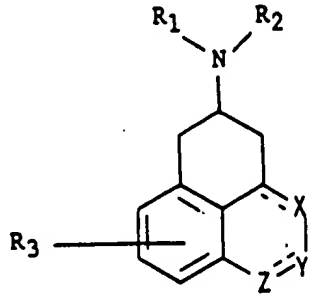


(D) hydrolysis to form the amine



CLAIMS

1. A compound of the formula



(I)

where one of X, Y and Z is -N(R_4)- and the remainder of X, Y and Z is -C(R_5)- or -C(O)-, and

when Z is -N(R_4)-, Y can be -C(R_5)- or -C(O)-, and X will be-C(R_5)-;

when Y is -N(R_4)-, X and Z will each be -C(R_5)-,

when X is -N(R_4)-, Y and Z will each be -C(R_5)-;

R_1 and R_2 are each hydrogen or C_1 to C_3-alkyl, or R_1 is hydrogen while R_2 is C_1 to C_4-alkyl, R_1 and R_2 can be taken together with the nitrogen to which they are bonded to complete an N-azetidinyl ring, or N-pyrrolidinyl ring, and N-piperidinyl ring or a N-morpholinyl ring;

R_3 is hydrogen or a substituent selected from the group consisting of

a halogen having an atomic number of from 9 to 35,

C_1 to C_3-alkyl,

C_1 to C_3-alkyloxy,

trifluoromethyl,

C_1 to C_3-alkyl-carbonyloxy,

phenylcarbonyloxy, or

benzylcarbonyloxy;

R_4 is part of a double bond when the ----- bond is double, or R_4 is hydrogen, C_1 to C_3-alkyl, or -C(O)R_6 when the ----- bond is a single bond;

R_5 is part of a double bond when the ----- bond is double, or R_5 is hydrogen when the ----- bond is a single bond;

R_6 is C_1 to C_3-alkyl or benzyl; or an acid addition salt thereof.

2. A compound according to Claim 1 wherein

Z is $-N(R_4)-$, Y is $-C(O)-$ and X is $-C(R_5)-$;

R_1 and R_2 are each hydrogen or C_1 to C_3-alkyl;

R_4 is hydrogen, so that the ----- bond between Y and Z is a single bond; and

R_5 is hydrogen, or an acid addition salt thereof.

3. A compound according to Claim 2 which is 3aS-trans-5-(dipropylamino)-3a,4,5,6-tetrahydro-1H-benzo[de]quinolin-2(3H)-one, or a pharmacologically acceptable salt thereof.

4. A compound according to Claim 3 wherein the compound is 3aS-trans-5-(dipropylamino)-3a,4,5,6-tetrahydro-1H-benzo[de]quinolin-2(3H)one, mono(4-methylbenzenesulfonate) salt.

5. A compound according to Claim 2 wherein the compound is 3aS-trans-5-amino-3a,4,5,6-tetrahydro-1H-benzo[de]quinolin-2(3H)one, or a pharmacologically acceptable salt thereof.

6. A compound according to Claim 5 which is a 3aS-trans-5-amino-3a-4,5,6-tetrahydro-1H-benzo[de]quinolin-2-(3H)-one hydrochloride salt.

7. A compound according to Claim 2 which is 3aS-trans-5-(N,N-dimethylamino)-3a,4,5,6-tetrahydro-1H-benzo[de]quinolin-2-(3H)-one, or a pharmacologically acceptable salt thereof.

8. A compound according to Claim 7 which is a 3aS-trans-5-(N,N-dimethylamino)-3a,4,5,6-tetrahydro-1H-benzo[de]quinolin-2(3H)-one hydrochloride salt.

9. A compound according to Claim 2 which is 3aS-trans-5-(N,N-dipropylamino)-3a,4,5,6-tetrahydro-1-propyl-1H-benzo[de]quinolin-2(3H)-one, or a pharmacologically acceptable salt thereof.

10. A compound according to Claim 9 which is a 3aS-trans-5-(N,N-di-

propylamino)-3a,4,5,6-tetrahydro-1-propyl-1H-benzo[de]quinolin-2(3H)-one hydrochloride salt.

11. A compound according to Claim 1 wherein Y is $-N(R_4)-$ and X and Z are each $-C(R_5)-$;

R_1 and R_2 are each C_1 to C_3-alkyl;

R_3 is hydrogen;

R_4 is absent so that the ----- bond between the position 1 carbon atom and the position 2 ring nitrogen is a double bond;

each R_5 is absent so that each ----- bond is a double bond;

or a pharmacologically acceptable salt thereof.

12. A compound according to Claim 11 which is 5,6-dihydro-N,N-dipropyl-4H-benz[de]isoquinolin-5-amine, or a pharmacologically acceptable salt thereof.

13. A compound according to Claim 12 which is a 5,6-dihydro-N,N-dipropyl-4H-benz[de]isoquinolin-5-amine, (E)-2-butenedioate salt.

14. A compound according to Claim 11 which is 5,6-dihydro-N,N-dimethyl-4H-benz[de]isoquinolin-5-amine, or a pharmacologically acceptable salt thereof.

15. A compound according to Claim 14 which is a 5,6-dihydro-N,N-dimethyl-4H-benz[de]isoquinolin-5-amine hydrochloride salt.

16. A compound according to Claim 1 wherein

X is $-N(R_4)-$, Y and Z are each $-C(R_5)-$;

R_1 and R_2 are each hydrogen or C_1 to C_3-alkyl;

R_3 is hydrogen;

R_4 is C_1 to C_3-alkyloxycarbonyl or C_1 to C_3-alkyl;

each R_5 is hydrogen, so that each of the ----- bonds is a single bond, or a pharmacologically acceptable salt thereof.

17. A compound according to Claim 16 which is ethyl trans-8-(dimethylamino)-2,3,7,8,9,9a-hexahydro-1H-benzo[de]quinolin-1-carboxylate,

or a pharmacologically acceptable salt thereof.

18. A compound according to Claim 17 which is ethyl trans-8-amino-2,3,7,8,9a-hexahydro-1H-benzo[de]quinolin-1-carboxylate, or a pharmacologically acceptable salt thereof.

19. A compound according to Claim 16 which is a trans-2,3,7,8,9a-hexahydro-N,N,1-trimethyl-1H-benzo[de]quinolin-8-amine, or a pharmacologically acceptable salt thereof.

20. A compound according to Claim 19 which is a 2,3,7,9,9a-hexahydro-N,N,1-trimethyl-1H-benzo[de]quinolin-8-amine hydrochloride salt.

21. A method for treating psychosis in a human or warm-blooded animal patient which comprises administering to such psychotic patient an anti-psychotic effective dose of a compound of Claim 1.

22. A method according to Claim 21 wherein the anti-psychotic compound of Claim 27 is one in which Z is $-N(R_4)-$, Y is $-C(O)-$ and X is $-C(R_5)$;

R_1 and R_2 are each hydrogen or C_1 to C_3-alkyl;

R_3 is hydrogen, so that the ----- bond between Y and Z is a single bond; and

R_5 is hydrogen,

or a pharmacologically acceptable salt thereof.

23. A method according to Claim 22 wherein the anti-psychotic compound is 3aS-trans-5-(dipropylamino)-3a,4,5,6-tetrahydro-1H-benzo-[de]quinolin-2(3H)-one, or a pharmacologically acceptable salt thereof.

24. A pharmaceutical composition useful in effective amount pharmaceutical dosage usage forms for treating a human or a valuable warm blooded animal patient suffering from psychotic disturbances which comprises a compound of Claim 1 mixed with a pharmacologically acceptable diluent.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 87/02866

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: C 07 D 221/14; A 61 K 31/435

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	C 07 D 221/00; C 07 D 209/00; A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	Journal of Medicinal Chemistry, volume 24, no. 10, October 1981, American Chemical Society, (US), J.G. Cannon et al.: "Future directions in dopaminergic nervous system and dopaminergic agonists", pages 1113-1118 see page 1113, column 2, lines 1-5; page 1114, column 2, lines 1-35 --	1,24
A	FR, A, 2471373 (ROUSSEL-UCLAF) 19 June 1981 see page 4, lines 22-25; claim 1 --------	1,24

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
8th February 1988	06 APR 1988
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	P.C.G. VAN DER PUTTEN

Form PCT/ISA/210 (second sheet) (January 1985)

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FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers ..*.. .... because they relate to subject matter not required to be searched by this Authority, namely:

* 21-23 See PCT Rule 39.i(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods

2. [ ] Claim numbers ....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international applicatuen as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 8702866 SA 19614

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 12/03/88
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR-A- 2471373	19-06-81	None	